The American Journal of Medicine



Luc Americani or mal a Medicine

Elime Caron B. Carons, C.D.

COLOREN STATED THE VOICE CONTRACTOR AND COMMENT AND COLOREN STATE OF THE PROSPECTALL NEW YORKS.

William Committee to the second terms

Pavid P. Barr Palls Arrive L. Brownser.

Pages 17th River Street

may have me as a society of the pages of the computer.

to the A. Brown, R. Leville, We benefit to the company of the comp

APPORATE MILIOR TOP ST.

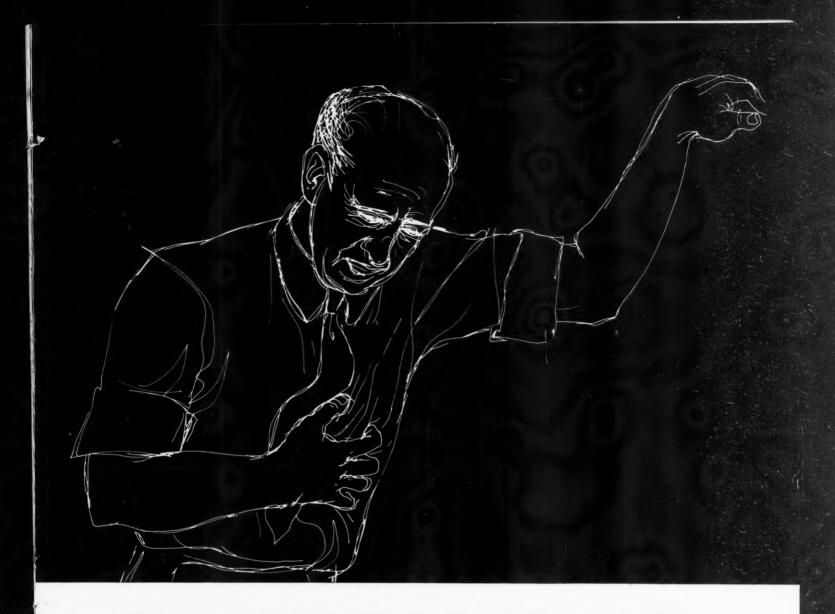
The street of th

THE REPORT OF THE PARTY OF THE

A constant of the constant of

Comment Control of French on the William State of the Control of French of William State of S

the workers of Roma. But a few arms to the contract of the con



You can prevent attacks in angina pectoris

Prolonged prophylaxis

Patients receiving Peritrate may obtain practical freedom from anginal attacks for from 4 to 5 hours with each dose. Russek and his colleagues¹ clearly showed that the patient-response to Peritrate was comparable to the effect produced by nitroglycerin...but the duration of Peritrate's action was "...considerably more prolonged."

Uncomplicated prophylaxi

Prolonged protection given by Peritrate spares the patient the anxiety of waiting for pain to strike. Besides invaluable psychological support, Peritrate brightens the objective clinical picture -significant EKG improvement may be seen^{1,2} and nitroglycerin need greatly reduced in most.³ A continuing schedule of only 1-2 tablets four times a day, before meals and at bedtime, will:

- **1.** reduce the number of attacks in almost 80 per cent of patients^{2,3}
- **2.** reduce the severity of attacks which cannot be prevented.

Available in 10 mg. tablets in bottles of 100, 500 and 5000.

References:

Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. 153:207 (Sept. 19) 1953.
 Winsor, T., and Humphreys, P.: Angiology 3:1 (Feb.) 1952.
 Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.



tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT



For ESSENTIAL HYPERTENSION

an
alliance
of the classic
and contemporary...

THEOMINAL R.S.

(Theominal with Rauwolfia serpentina)

Combines for synergistic action:

Theominal itself has been widely prescribed for essential hypertension for several decades. The addition of Rauwolfia serpentina alkaloids—purified alseroxylon fraction—to the well established Theominal formula represents a substantial improvement.

With the use of Theominal R.S., objective and subjective improvement can be obtained in a large percentage of hypertensive patients. There is mild and gradual but sustained reduction of excessive blood pressure and pulse rate to near normal levels. Striking symptomatic improvement occurs concurrently: alleviation of congestive headache, vertigo, dyspnea, nervous irritability, apprehension and insomnia.

With Theominal R.S. medication the antihypertensive action of Luminal and theobromine may be evident in a few days, whereas a week or more may elapse before the Rauwolfia component exhibits its maximum effectiveness. However, the sense of well being due to Rauwolfia is experienced within a few days of medication and usually precedes the development of the maximum antihypertensive effect. Theominal R.S. is well tolerated.

DOSAGE: The usual dose of Theominal R.S. is 1 tablet two or three times daily. When improvement has been maintained for a time, the dose may be reduced or medication suspended occasionally until its resumption is indicated.

HOW SUPPLIED: Theominal R.S. is supplied in bottles of 100 tablets.



CONTENTS

The American Journal of Medicine

Vol. XVII NOVEMBER, 1954 No. 5

T 11.		1
Edit	aria	I
I AULLE	or car	ı,

Enzymes and Templates in Bone Salt Formation . . . Alexander B. Gutman 585

Clinical Studies

QRS Complex Deformity of Myocardial Infarction in the Human Subject
ROBERT P. GRANT AND RAYMOND H. MURRAY 587

The authors apply vector principles to an analysis of the QRS complex deformities recorded in conventional electrocardiograms generally accepted as diagnostic of myocardial infarction. The electrical characteristics of the QRS complex are first considered in normal subjects, then in seventy-seven cases exhibiting typical "infarct Q waves." From this analysis comes a reformulation in electrical terms of the Q wave criteria currently designated as diagnostic of infarction. The authors then proceed to a study in 190 cases of the effects of infarction on the QRS electrical field by comparing postinfarction with preinfarction tracings compiled from the routine electrocardiographic files of a number of hospitals. While many limitations in the diagnosis of myocardial infarction by conventional technics are made apparent by the authors, the current criteria do not, on the whole, fare too badly in this searching analysis. Nevertheless, the whole discussion gives so much perspective to hackneyed empirical ECG patterns that the paper should be required reading for those interested in interpretation.

Studies on the Mechanism of Ventricular Activity

VIII. Genesis of the Coronary QS Wave in Through-and-Through Infarction
Myron Prinzmetal, Rexford Kennamer and Morton Maxwell 610

IX. "Mural-type" Coronary QS Wave

MORTON MAXWELL, REXFORD KENNAMER AND MYRON PRINZMETAL 614

In the first paper the investigators find that direct epicardial leads in authenticated through-and through myocardial infarction in dogs yield QS complexes identical with the cavity and subjacent intramural QS complex. These results accord with classic theory, originated by Wilson, which explains the coronary QS wave by assuming transmission of the negative cavity potential without alteration through dead infarcted tissue.

In the second paper, however, it is pointed out that typical coronary QS waves may be recorded over infarcted myocardium which is, in part, still viable. In such instances of "mural-type" QS waves the complexes recorded in epicardial, intramural and cavity leads showed differences in timing and/or configuration and therefore unaltered transmission of negative cavity potentials was not occurring. The authors presume that in such circumstances the coronary QS wave, along with a variety of other abnormal complexes, reflects only partial destruction of the outer layers of the ventricle. Clinical implications in respect to interpretation of QS waves in patients with coronary artery disease are pointed out.

Contents continued on page 5

relieve pain, headache, fever promptly and safely

APAMIDE®

(N-acetyl-p-aminophenol, Ames. 0.3 Gm.)

4

direct-acting analgesic-antipyretic...
no toxic by-products...

APAMIDE-VES

TRADEMARK

(Buffered Nacetyl-p-aminophenol, Ames, 0.3 Gm.

effervescing analgesic-antipyretic... speeds relief...assures fluid intake

APROMAL

(acetylcorbromal and N-acetyl-p-aminophenal, Ames, 0.15 Gm. ea.

sedative-analgesic-antipyretic...
calms patients and relieves pain



COMPANY, INC • ELKHART, INDIANA

Ames Company of Canada, Ltd., Toronto

39554

CONTENTS

The American Journal of Medicine

Vol. XVII NOVEMBER, 1954 No. 5

Contents continued from page 3

Value of Rauwolfia Serpentina in the Hypertensive Patient Frank A. Finnerty, Jr. 629

This is a study of the place of Rauwolfia in the management of essential hypertension; when used alone in place of barbiturate sedation in treating milder forms of the disease, and in combination with other more potent but also more toxic hypertensive agents to make possible reduction in dosage of these agents. Observations were made in eighty-nine patients, all ambulatory, and were sufficiently prolonged and controlled (placebos) to have some meaning. The results confirm the general impression that Rauwolfia preparations, given alone, are efficacious in the management of the milder degrees of essential hypertension. Moreover, conjoint administration often permits significant reduction in dosage of veratrum, hexamethonium and hydralazine preparations, with lessening of side reactions.

Esophageal Varices in Non-cirrhotic Patients. Esophagoscopic Study Lt. Col. Eddy D. Palmer and Irving B. Brick 641

Granted that roentgenographic technics during life, and necropsy subsequently, probably underestimate the incidence of esophageal varices, the frequency here recorded by competent esophagoscopists is nevertheless rather startling. For example, varices were found in four of seven patients with chronic congestive failure in whom liver biopsy (if it can be relied upon under such circumstances to yield a representative sample) indicated little or no fibrosis. Perhaps there is need for sharper differentiation between the limits of distensibility of veins in congestive failure and what the clinician considers to be hazardous varix formation.

Effect of the Oscillating Bed and Tilt Table on Calcium, Phosphorus and Nitrogen Metabolism in Paraplegia Derek M. Wyse and C. J. Pattee 645

Ambulation appears to be the most effective way to restore metabolic equilibrium in paraplegics, but in the long interval before this is possible such devices as the oscillating bed and the tilt table may be tried. The experience here recounted is rather discouraging in discounting favorable effects on calcium, phosphorus and nitrogen balance. It would appear, however, that further efforts should be made in the direction of inducing muscular contractions in the paralyzed limbs.

An Abnormal Lipid-like Material and Carbohydrate in the Sera of Patients with Multiple Myeloma . Bernard A. Sachs, Paxton Cady and George Ross 662

Paper electrophoresis, with appropriate staining, revealed the presence of lipids and carbohydrates, in association with abnormal proteins, in the sera of patients with multiple myeloma. These do not occur in the patterns of normal subjects, or, apparently, in other diseases. The inference drawn is that multiple myeloma involves disturbances in lipid and carbohydrate as well as protein metabolism, and that these may be related to the occurrence of amyloid deposits in this disorder.

Contents continued on page 7

for sedation

tranquilization without hypnosis

RAU-SED

SOUIBB RESERPINE

the chief sedative alkaloid of rauwolfia

0.1 and 0.25 mg. tablets, bottles of 100 and 1,000. 0.5 mg. tablets, bottles of 50 and 500.

in hypertension

RAUDIXIN

SQUIBB RAUWOLFIA

contains all the alkaloids of rauwolfia

50 and 100 mg. tablets, bottles of 100 and 1,000.

SQUIBB

"RAU-SED" AND "RAUDIXIN" ARE SQUIBB TRADEMARKS

CONTENTS

The American Journal of Medicine

Vol. XVII NOVEMBER, 1954 No. 5

Contents continued from page 5

Serum Proteins and Lipoproteins in Multiple Myelomatosis

LENA A. LEWIS AND IRVINE H. PAGE 670

The sera of twenty-four patients with multiple myeloma were analyzed both electrophoretically and by ultracentrifugation, and the two sets of protein patterns then compared. The usual electrophoretic abnormalities were observed but these did not appear to be associated with striking changes in the lipoproteins.

Disappearing Bones: A Rare Form of Massive Osteolysis. Report of Two Cases, One with Autopsy Findings

L. W. GORHAM, A. W. WRIGHT, H. H. SHULTZ AND F. C. MAXON, JR. 674

The authors call attention to a rare and probably heterogeneous group of cases characterized by slow but extensive disappearance of bone, with startling roentgenograms contrasting sharply with the locally deformed but otherwise usually quite healthy patient. Most of these lesions prove ultimately to be due to the presence of an angiomatous, usually hemangiomatous, mass.

Review

Respiratory Recovery Rates after Poliomyelitis

JOHN F. MARCHAND AND AARON T. MARCUM 683

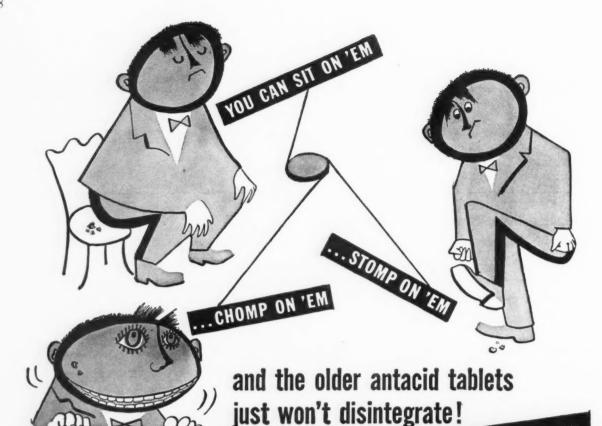
This article is concerned with the management of postpoliomyelitis paralytics with respiratory crippling, of whom there are over 1,000 in this country. Detailed respiratory schedules are described in twenty illustrative cases. Emphasis is placed on graded muscle re-education to develop use of accessory respiratory muscles. The need of psychologic as well as physical weaning from respirator aids is stressed. The results that can be obtained by careful, patient, individualized planning, so patent in this article, are remarkable indeed.

Seminars on Antihypertensive Drugs

Rauwolfia in the Treatment of Essential Hypertension Robert W. Wilkins 703

The Rauwolfia preparations have already won a distinctive place in the management of essential hypertension because of their slow, moderate antihypertensive effect, which usually is readily controlled, and a minimum of serious side reactions. They can be used alone in milder cases, with gratifying symptomatic response and fall in blood pressure. In more severe cases they are a useful adjunct or background agent to be employed with more potent antihypertensive agents, which can then be given in lower dosage and with fewer side reactions.

Contents continued on page 9



now TREVIDAL® tablets

break up in less than a minute, assuring rapid yet prolonged relief of hyperacidity.

EACH TREVIDAL TABLET CONTAINS:

Balance of ingredients avoids constipation, diarrhea, or alkalosis

Unique vegetable mucin supplies protective coat to irritated stomach lining

Binder controls and extends antacid activity

Aluminum hydroxide gel, dried ... 90 mg.

Magnesium trisilicate ... 150 mg.

Magnesium carbonate ... 60 mg.

Calcium carbonate ... 105 mg.

Regonol* ... 100 mg.

Egraine* ... 45 mg.

AVAILABLE IN BOXES OF 100 TABLETS, SPECIALLY STRIPPED FOR EASY CARRYING.

Cyamopsis tetragonoloba gum Trade Marks



Organon inc. · orange, n. J.

CONTENTS

The American Journal of Medicine

Vol. XVII NOVEMBER, 1954 No. 5

Contents continued from page 7

Treatment of Hypertensive Disease with Hydralazine. Comparison of Its Action with That of Low Sodium Diet in Hospitalized Patients

ALBERT J. STUNKARD, GERALD H. EURMAN, MORTON WACHSPRESS AND ARTHUR R. WERTHEIM

712

The authors present the results of adequately controlled, sufficiently prolonged and critically evaluated observations on the effects of hydralazine (apresoline®) in twenty-five patients with significant hypertension persisting throughout prolonged hospitalization. In seventeen patients the diastolic blood pressure fell significantly. There was regression of retinopathy in some cases. Improvement in cardiac failure, heart size and electrocardiographic abnormalities was disappointing in most cases. Side reactions, particularly headache, were not too distressing but required careful regulation of dosage and supplementary medication. It is concluded that hydralazine affords somewhat less effective antihypertensive therapy than stringent sodium restriction but is a much simpler form of management.

Conference on Therapy

Conference on Therapy (Cornell University Medical College)—This conference is concerned primarily with the validity of procedure for clinical assessment of newly introduced therapeutic agents—a subject of prime importance, to be sure—but many of the points made apply also to clinical evaluation of any drug, old or new. The significance of the discussion therefore extends directly into the daily practice of every physician. This broad and vital aspect of medical practice is by no means exhaustively treated but among the points brought out are the effect of mood of the patient on patient response to drugs, the place of the placebo, the importance of the double blindfold technic in clinical pharmacology, the role of "honest subjectivity" of the evaluating physician, the limitations of statistical analysis of results and the importance of experimenal design to eliminate conscious or unconscious bias.

Clinico-pathologic Conference

Substernal Goiter, Thyrotoxicosis, Tracheal Compression and Pulmonary Disease . 728

Clinico-pathologic Conference (Washington University School of Medicine)—A most interesting case offering unusual difficulties in diagnosis and additional support for the old dictum that carcinoma of the thyroid gland rarely is associated with hyperthyroidism.

Contents continued on page 11

IN TENSION AND HYPERTENSION

sedation without hypnosis

RSerpasil*

(reserpine CIBA)

A pure crystalline alkaloid of rauwolfia root first identified, purified and introduced by CIBA

In anxiety, tension, nervousness and mild to severe neuroses—as well as in hypertension—SERPASIL provides a nonsoporific tranquilizing effect and a sense of wellbeing. Tablets, 0.25 mg. (scored) and 0.1 mg.

CIBA

SUMMIT, N. J.

CONTENTS

The American Journal of Medicine

Vol. XVII NOVEMBER, 1954 No. 5

Contents continued from page 9

Case Reports

Necrotizing Angiitis Associated with Chronic Ulcerative Colitis

Fred Wasserman, Arthur Krosnick and Henry Tumen 736

In this intriguing and thought-provoking case what appears to be typical non-specific ulcerative colitis occurred together with a diffuse arteritis and associated features consistent with the concept of allergic granulomatous angiitis. The possible relationship of these two disorders, and of the latter to drug sensitivity, is discussed interestingly.

Normal Bone Marrow in Untreated Pernicious Anemia

BURTON COMINSKY AND CATHERINE I. HOLAVKO 74

The point of this paper is that in bona fide cases of pernicious anemia with evidences of only mild anemia the bone marrow may contain so few megaloblasts as to escape detection in routine marrow aspiration. Such patients may nevertheless exhibit distinct and progressive neurologic changes. Since the response to vitamin B_{12} is good, recognition in time is important. Four illustrative cases are cited.

Announcement

The Editorial Board is pleased to announce that the American Medical Writers' Association has selected The American Journal of Medicine as the 1954 recipient of its Honor Award for Distinguished Service in Medical Journalism. The Citation reads, "for accuracy, clarity, conciseness and newness of information; for excellence of design, printing and illustrations, and for distinguished service to the Medical Profession."

This honor is a tribute to the publishers, who have spared no effort or expense in publication; to our editorial assistants, for their meticulous editing of manuscripts; and particularly to the many contributors to the Journal, who each share in the event.

THE EDITOR

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.

SQUIBB ANNOUNCES TWO IMPORTANT

THE FIRST antifungal antibiotic

MYCOSTATIN

SQUIBB NYSTATIN

Highly effective for prevention and treatment of intestinal moniliasis

The intestinal flora of patients treated with oral antibiotics, particularly the broad spectrum preparations, undergoes profound changes. In many cases there is a strong overgrowth of Candida (monilia), and the extent of overgrowth seems to be proportional to the amount of the antibiotic taken. This phenomenon does not necessarily lead to clinical moniliasis, but a considerable number of patients with an overgrowth of Candida have intestinal symptoms, including diarrhea, ulceration, anal fissure, and persistent pruritus.

When such effects are due to Candida, they can be prevented by Mycostatin. Established monilial infection of the gastrointestinal tract can be cleared up by Mycostatin in 24 to 48 hours.

Dose: 500,000 units t.i.d.; to be doubled if intestinal fungi are not suppressed. Mycostatin is well tolerated by nearly all patients, and is compatible with the commonly used antibiotics.

500,000 unit tablets Bottles of 12 and 100

'Mycostatin' is a Squibb trademark

NEW ANTIBIOTICS

BROAD SPECTRUM ANTIBIOTIC OF CHOICE

STECLIN

HYDROCHLORIDE

Squibb Tetracycline Hydrochloride

Steclin is the newest broad spectrum antibiotic.

- Fewer side effects, better tolerated than oxytetracycline or chlortetracycline.
- · Greater stability in blood serum,
- Efficient distribution to tissues and body fluids.
- Fully effective blood levels.

50 and 100 mg. capsules Bottles of 25 and 100 250 mg. capsules Bottles of 16 and 100 **SQUIBB**

The range of clinical usefulness of Steclin is similar to that of oxytetracycline and chlortetracycline. It is often superior to its analogs because therapeutic blood levels are achieved with fewer gastrointestinal side effects.

As with all broad spectrum antibiotics, overgrowth with nonsusceptible organisms, particularly monilia, may occur.

'Steclin' is a Squibb trademark



prescribe Bonadoxin*

BRAND OF MECLIZINE HCI, PYRIDOXINE HCI

tablets

New combination attacks nausea and vomiting of pregnancy on two planes:

The Symptomatic Plane-Bonadoxin contains meclizine-the safe, longeracting antiemetic with highly specific vestibular effects.

The Metabolic Plane—Bonadoxin contains pyridoxine—the enzyme-essential vitamin for which requirements are markedly increased during the first trimester. Its presence in high dosage helps restore proper carbohydrate metabolism, glycogen storage and hepatic function, thus correcting physiological derangements associated with "morning sickness."

Clinical results¹: Abolished vomiting in 40 of 41 gravid women, eliminated nausea in 30 of 41. Less than 3% side effects. Dosage: 1 or 2 tablets, at bedtime. Larger doses if necessary. Supplied: Bottles of 25, prescription only. Each Bonadoxin Tablet contains 25 mg. meclizine hydrochloride, 50 mg. pyridoxine hydrochloride.

1. Garrett, T. A.: Personal communication

#TRADEMARK



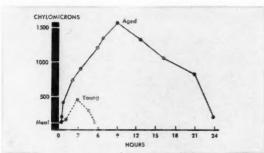
Ethical Pharmaceuticals for Needs Basic to Medicine 536 Lake Shore Drive, Chicago 11, Illinois

ATHEROSCLEROSIS

Revised concepts of etiology predicate new therapeutic approach

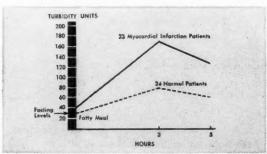
Recent studies attach increasing importance to the particle size and physical characteristics of certain blood lipids, rather than total serum cholesterol as such, in the genesis of atherosclerosis. Assays of neutral fat particles in the blood (chylomicra) following fat ingestion, and the closely related concentration of low-density "giant" lipoprotein molecules, show much greater correlation with clinical atherosclerosis than either the serum cholesterol level per se or the cholesterol-phospholipid ratio.

It has also been shown that (1) a high incidence of hypercoagulability and low blood heparin levels exist in patients with cardiovascular disease and atherosclerosis; (2) circulating heparin tends to decrease with age; and (3) an inverse ratio exists between the concentration of giant lipoprotein molecules and serum heparin levels.



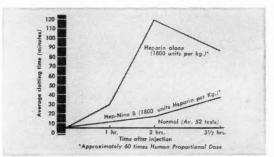
Chylomicron curves of fasting young and old subjects after a Standard fat meal. After Becker et al: Science 110:529, 1949.

Parenterally administered, heparin exerts a profound "clearing" action on chylomicra and the giant molecules. This action is independent of heparin's anticoagulant effect. In the treatment of atherosclerosis, the addition of choline and specific B vitamins appears to enhance heparin's efficacy. Vitamin B₁₂ and folic acid aid in the synthesis of labile methyl groups and the transmethylation process. Choline specifically increases the phospholipid turnover, and parenterally administered, it has been shown to have a distinct vasodilating effect. Most significantly, however, choline decreases the anticoagulant action of heparin, when both drugs are administered simultaneously at the same site, without impairing the clearing effect of heparin. Thus the use of heparin for atherosclerotic diseases is rendered safe as a routine office procedure, without necessity for periodic clotting time determinations.



Fat Tolerance in Myocardial Infarction and Control Patients. From data of Schwartz et al: JAMA 149:364, 1952.

A preliminary clinical report $^{\circ}$ on HEP-NINE B—which combines heparin, choline, vitamin B_{12} , folic acid and niacinamide for intramuscular injection—indicates that the combination offers considerable promise in a variety of conditions in which atherosclerosis plays a part, such as angina pectoris, myocardial infarction, coronary disease, related kidney and liver diseases, diabetes mellitus, and certain



Comparison of effects of Hep-Nine B and Heparin alone on clotting time

cases of obesity. Pharmacologic studies showed no significant effect on coagulation time, even in dosage far exceeding that recommended. Chylomicron concentration was reduced promptly in all cases following a single injection, ranging from a minimum 29% reduction (diagnosis: anterior myocardial infarction) to a maximum of 100% (diagnosis: multiple cerebral thrombosis). In patients selected for a history of myocardial infarction or diabetes, the atherogenic index as determined by the Gofman Serum Lipoprotein Test was materially reduced in all cases without benefit of diet restriction. Of 30 patients with recurrent angina pectoris, 23 experienced marked reduction in frequency and severity of episodes. Nitroglycerine requirements were reduced and exercise tolerance was increased in all cases. No patient suffered coronary occlusion or myocardial infarction during the period of study.

Hep-Nine B

Represents a safe office procedure for the treatment of atherosclerosis. Hospitalization and periodic clottingtime determinations are not required. Each cc. contains:

Heparin Choline		(2500		mg.
Vitamin Folic Aci	B ₁₂			mcg.
Niacinan		*******		mg.

Recommended dosage is 1 or 2 cc. intramuscularly, once or twice weekly. Supplied in 10 cc. multiple dose vials.

The Columbus Pharmacal Company Columbus 15, Ohio

Send for complete information and references.

*Read, J. T., and Obetz, R. C.: Clinical Experience with Parenteral Heparin-Lipotropic Therapy in Cardiovascular Diseases. Obio State M. J. (In press).



ELECTRON PHOTOMICROGRAPH

Diplococcus pneumoniae 35,000 x

Diplococcus pneumoniae (Streptococcus pneumoniae) is a Gram-positive organism commonly involved in

lobar—and bronchopneumonia • chronic bronchitis • mastoiditis • sinusitis

otitis media • and meningitis.

It is another of the more than 30 organisms susceptible to

PANMYCIN

100 mg. and 250 mg. capsules

TRADEMARK, REG. U. S. PAT. GFF.

Upjohn

designed for the Pain of most patients.

Each Capsule Contains:

MECHANISM OF ACTION OF PHENAPHEN WITH CODEINE

ASPIRIN 162 mg. (21/2 gr.)

PHENACETIN 194 mg. (3 gr.)

Analgesic Synergists for greater pain relief than that afforded by either alone.

PHENOBARBITAL 16.2 mg. (1/4 gr.)

Sedative Potentiator to allay anxiety and blunt pain perception.

Analgesic Reinforcement for mutual syn-

16.2 mg. or 32.4 mg. (1/4 or 1/2 gr.) HYOSCYAMINE

CODEINE

PHOSPHATE

SULFATE 0.031 mg. (1/2000 gr.)

ergism with other analgesic-sedative ac-Cholinergic Depressant to relieve spasm

and counteract constipation-nausea tendency of codeine.

More effective analgesicsedative action.

More satisfactory analgesic action with low codeine dosage.

MAXIMUM

SAFE

ANALGESIA



A HE ROBING CO., INC. RICHMOND 20, VAT

International Superintered

Superior clinically proved

W...it must be concluded Robitussin was the effective cough medicine of choice over the recognized remedies ammonium chloride and terpin hydrate...significantly superior to the other preparations studied." -Cass, L. J. & Frederik, W. S.: Am. Pract. & Dig. Treat. 2:844, 1951.

"The excellent results fin treating whoop ing cough with Robinssinl ... were a great Levelation. .. the severity and number of cough spagns have been reduced at least 50% (compared with Preparations Previously used and the duration definitely shortened. Blanchard. K. & Ford, R. A.: To be published.

> antitussive demulcent expectorant

Robitussin[®]

ROBITUSSIN

A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA Robins



Each teaspoonful (5 cc.) contains: Glyceryl guaiacolate 100 mg. and desoxyephedrine hydrochloride 1 mg. in a palatable syrup vehicle.

potent hematinic...

Fully adequate for the oral treatment of pernicious anemia and other macrocytic anemias.

Meets U.S.P. specifications.

Contains extra amounts of B

Patterned after Spies' basic formula,* provides a full complement of other essential or accessory hemopoietic factors for optimum response in the treatment of the common anemias.

Recommended daily dosage (3 capsules) contains:

Vitamin B_{12} with intrinsic factor concentrate 1 U.S.P. Unit

"CLUSINTRIN"

for effective, practical antianemia therapy

Indications: Treatment of pernicious anemia and other macrocytic hyperchromic anemias; microcytic hypochromic anemia.

Availability: No. 316 — Supplied in bottles of 100 and 1,000.

*Spies, T. D.: J.A.M.A. 145:66 (Jan. 13) 1951.



Ayerst Laboratories, New York, N. Y. • Montreal, Canada



SUR-BEX®

(Abbott's Vitamin B Complex Tablets)

or SUR-BEX with Vitamin C

(Contains 150 mg. of ascorbic acid in addition to the B complex factors below)

just 1 SUR-BEX tablet a day supplies:

Thiamine Mononitrate
Riboflavin
Nicotinamide
Pyridoxine Hydrochloride

Vitamin B12 (as vitamin B12 concentrate)
Pantothenic Acid (as calcium pantothenate)
Liver Fraction 2, N.F.
Brewer's Yeast, Dried

6 mg.

6 mg.

30 mg.

1 mg.

2 mcg.

10 mg.

300 mg.

150 mg.





Every patient whose symptoms are less clearly defined, yet equally distressing . . . for example, easy fatigability, tachypnea, insomnia, headache. Frequently, these symptoms of declining ovarian function are not identified as such because they occur long before or even years after menstruation ceases. The patient exhibiting these symptoms may be expected to respond to estrogen therapy. "Premarin" presents the complete equine estrogen-complex as it and distinctive "sense of well-being." It is tasteless and odorless. "Premarin," estrogenic substances (water-soluble), also known as conjugated estrogens (equine), is supplied in tablet and liquid form.



Rauwolfia serpentina as sole therapy

For every patient with mild, moderate, or labile hypertension

In addition to dropping the blood pressure moderately, Rauwolfia serpentina produces marked, often dramatic, subjective improvement. It relaxes the emotionally tense patient, gradually inducing a welcome state of calm tranquility.

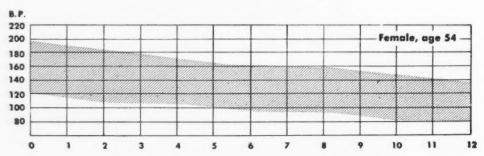
Headache, tinnitus and dizziness are greatly relieved, and the discomfort of palpitation is usually overcome. Hence, it usually suffices as sole medication in mild, moderate and labile hypertension, especially when the emotional element is a prominent factor.

Rautelessin Purified Rauwolfia Serpentina Alkaloids

Rautensin produces the typical hypotensive, sedative, and bradycrotic effects characteristic of this important new drug. Each tablet contains 2 mg. of the alseroxylon fraction, a highly purified alkaloidal extract entirely free of inert material. The alseroxylon fraction is tested in dogs for its ability to lower blood

pressure, produce sedation, slow the pulse.

The initial dose of Rautensin is 2 tablets (4 mg.) daily for 30 to 60 days. After the full therapeutic effect has been established, the daily intake is dropped to 1 tablet (2 mg.) daily. Side actions are rare and there are no known contraindications.



Weeks of therapy. Rautensin, 4 mg. daily. Marked subjective improvement.

SMITH-DORSEY · Lincoln, Nebraska A Division of THE WANDER COMPANY

Rauwolfia serpentina in combination

For the patient with chronic, severe, or fixed hypertension

Most cardiologists today assert that in severe or fixed essential hypertension, combination therapy is more efficacious than any single drug alone. The combination of Rauwolfia serpentina and Veratrum viride is especially favored since it results in an additive, if not a synergistic, effect. In this combination, the dosage requirements of veratrum are significantly reduced, hence the incidence of side effects is greatly minimized.

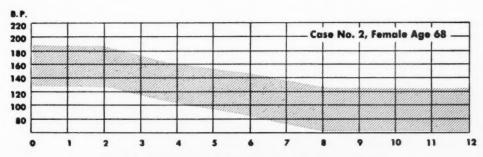
Rawera

Rauwolfia Serpentina and Veratrum Viride Alkaloids

Each Rauvera tablet combines 1 mg. of the alseroxylon fraction of Rauwolfia serpentina and 3 mg. of alkavervir, a highly purified alkaloidal extract of Veratrum viride. The potent hypotensive action of veratrum is thus superimposed on the desirable influence of Rauwolfia. Rauvera leads to a substantial

reduction in blood pressure and marked subjective improvement, hence produces excellent results in chronic, severe, and fixed essential hypertension.

The average dose of Rauvera is 1 tablet 3 times daily, after meals, at intervals of no less than 4 hours.



Weeks of therapy. Rauvera, 4 tablets daily. Note blood pressure response.

SMITH-DORSEY · Lincoln, Nebraska A Division of THE WANDER COMPANY



control of salt-retention edema

maintained by



CUMERTILIN

[Brand of Mercumatilin]

TABLETS

effective oral diuretic
...with no significant
gastrointestinal irritation

In a recent study, CUMERTILIN Tablets alone proved effective and well tolerated in maintaining cardiac compensation in most ambulant patients with congestive heart failure. Long-term treatment for periods ranging up to 658 days was accomplished "with no significant gastrointestinal reactions."

Dosage is 1 to 3 tablets daily as required.
Supplied as orange tablets, each containing
67.7 mg. CUMERTILIN (equivalent to 20 mg. each
of mercury and theophylline). Also available
as CUMERTILIN Sodium Injection, 1- and 2-cc.
ampuls, 10-cc. vials.

Samples? Just write to:

Endo

ENDO PRODUCTS INC. Richmond Hill 18, New York

1. Pollock, B. E., and Pruitt, F. W.: Am. J. M. Sc. 226:172, 1953.





rapid relief

for coughs from colds or allergies

AMBENYL

AMBENYL owes its special value to the action of two outstanding antihistaminics combined with other valuable agents. Benadryl, noted for its antihistaminicantispasmodic action, and Ambodryl, with its high antihistaminic activity, act together to make coughing patients more comfortable. The antispasmodic, antiallergic, decongestant, and demulcent actions of pleasant-tasting AMBENYL

- quiet the cough reflex
- facilitate expectoration
- decrease bronchospasm
- relieve mucosal congestion

AMBENYL contains in each fluidounce:

Ambodryl hydrochloride 24 mg. (bromodiphenhydramine hydrochloi Parke-Davis)

Benadryl hydrochloride 56 mg. (diphenhydramine hydrochloride.

Dihydrocodeinone bitartrate . . . % gr.

Ammonium chloride 8 gr. Potassium gualacolsulfonate . . . 8 gr.

Menthol q.s.

Supplied in 16-ounce and 1-gallon bottles.

dosage Every three or four hours-adults, 1 to 2 teaspoonfuls; children, % to 1 teaspoonful.



Parke, Davis + Company



PHOTOGRAPH BY CHARLES KERLES

Puts the gouty arthritic "on the road" again...

BENEMID

PROBENECID

Typical of the dramatic results with BENEMID in chronic gouty arthritis is the case of "J. B. . . . bedridden two months with continued pain. . . . At the end of probenecid therapy, he was able to walk unaided and drive his automobile."

BENEMID "increases the excretion of uric acid by diminishing its tubular reabsorp-

tion."² It helps prevent tophi, decreases those already present³—thus diminishes inflammation and muscular spasm.² Toxic reactions are unusual.

Quick Information: Available in 0.5 Gm. tablets. Dosage: 1 to 4 tablets daily. Contraindications: Renal impairment.

References: 1. J.A.M.A. 149:1190, 1952. 2. J.A.M.A. 154:216, 1954. 3. Geriatrics 8:606, 1953.



Staphylococcus aureus 35,000 x

Staphylococcus aureus (Micrococcus pyogenes var. aureus) is a Gram-positive organism commonly involved in a great variety of pathologic conditions, including pyoderma • abscesses • empyema • otitis • sinusitis • septicemia bronchopneumonia • bronchiectasis • tracheobronchitis • and food poisoning.

It is another of the more than 30 organisms susceptible to

PANMYCIN

100 mg. and 250 mg. capsules

*TRADEMARK. REG. U. S. PAT. OFP.

Upjohn

Pamin

REGISTERED TRADEMARK FOR THE UPJOHN BRAND OF METHSCOPOLAMINE BROMIDE

Back Issues Wanted

(MUST BE IN PERFECT CONDITION)

THE AMERICAN JOURNAL OF MEDICINE

will pay
\$1.00 per copy for the following issues:

July 1946 May 1947 August 1946 June 1947 September 1946 November 1947 October 1946 January 1948 November 1946 February 1948 June 1949 December 1946 January 1947 August 1949 February 1947 March 1947 September 1949 January 1950 April 1947 February 1950

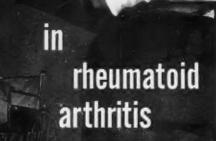
January 1951
April 1951
May 1951
June 1951
July 1951
August 1951
January 1953
February 1953
March 1953
February 1954

Send to

THE AMERICAN JOURNAL OF MEDICINE, INC.
49 West 45th Street New York 36, N. Y.



BRONURAL the non-barbiturate sedative prescribe Bromural for daytime sedation, one tablet every three to five hours. For sleep, 2 or 3 tablets upon retiring or when wakeful during the night. BROMURAL, brand of Bromisovalum, monobromisovalerylurea, is available as 5-grain tablets and in powder form. Bilhuber—knoll Corp., ORANGE, NEW JERSEY



adrenocortical hormone therapy can transform virtual helplessness into active ambulation)

tablets brand of hydrocortisone available as scored tablets,

also available

10 mg. and 20 mg.

TERRA-CORTRIL* Topical Ointment
TERRA-CORTRIL* Ophthalmic Suspension New, easier-to-write, easier-to-remember names

CORTRIL Topical Ointment

CORTRIL Acetate Ophthalmic Ointment

CORTRIL Acetate Aqueous Suspension for intra-articular injection

Pfizer

PFIZER LABORATORIES

Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N.Y.

> *brand of oxytetracycline and hydrocortisone

relieve
cold symptoms...
curb
complications

CORICIDIN®
with
PENICILLIN

150,000 units Penicillin G Procaine

· analgesic · antibiotic · antihistaminic · antipyretic



NOW the safest agent
yet developed for
decisive control of BLOOD PRESSURE
with 5 important firsts

UNITENS

brand of cryptenamine

Unitensen is recommended for the patient who needs more than tranquilizing effects. It produces positive, sustained falls in blood pressure.

This is what Unitensen Tablets do . . . and with unparalleled safety
These patients experienced sustained control of blood pressure levels over prolonged periods of time.

Summary of Casé Histories-Series A*

Age—Sex	BP-mm. Hg. BEFORE	BP—mm. Hg. AFTER
64-M	190/115	140/90
37-M	200/130	130/85
48-M	230/140	140/100
46-M	220/140	160/110
41-M	210/140	155/110
43-M	200/120	160/110
26-M	230/130	180/120
44-M	220/130	175/120
46-M	220/120	162/90

FIRST IN MAINTAINING DECISIVE BLOOD PRESSURE CONTROL

The sole therapeutic agent in Unitensen Tablets is cryptenamine—a potent blood pressure lowering alkaloid fraction isolated by the research staff of Irwin, Neisler

& Company. In the majority of cases (see chart at left), cryptenamine will lower blood pressure decisively, and will control blood pressure at the lower levels for prolonged periods of time.

FIRST IN SAFETY

Unitensen Tablets exert a central action on the blood pressure lowering mechanism. Circulatory equilibrium is not disrupted. Improved circulation and improved work of the heart are often attained, along with the decisive fall in blood pressure.

Unitensen Tablets have no sympatholytic or parasympatholytic action. Ganglionic blocking does not occur. Unitensen Tablets do not cause postural hypotension and collapse, an ever-present risk with other potent blood pressure lowering drugs. Renal function is not impaired.

FIRST WITH DUAL ASSAY

Unitensen is biologically standardized twice, first for hypotensive response and, second, for side effects (emesis) in the dog so that a safe therapeutic range between the two is assured. In extensive clinical trials only a few isolated cases exhibited occasional vomiting.

Unitensen Tablets do not cause the serious side effects common to widely used synthetic hypotensives. Unitensen Tablets can be given over long periods of time with entire dependability. Cumulative effects have not been noted.

FIRST IN SIMPLE DOSAGE

Start with 2 tablets daily, given immediately after breakfast and at bedtime. If more tablets are needed, include an afternoon dose at 1 or 2 p.m.

FIRST IN ECONOMY

TANNATE TABLETS

Bottles of 50, 100,

500 and 1000.

Because of lower dosage, Unitensen Tablets save your patients $\frac{1}{3}$ to $\frac{1}{2}$ over the cost of other potent blood pressure lowering agents.

*Ester alkaloids of Veratrum viride obtained by an exclusive Irwin-Neisler nonaqueous extraction process. †Equivalent to 260 Carotid Sinus Reflex Units.

IRWIN, NEISLER & COMPANY

DECATUR, ILLINOIS

the key

to efficient,

well-tolerated

diuretic therapy

AMPOULES DICURIN PROCAINE SOLUTION

May be given subcutaneously or intramuscularly with no pain or stinging on injection. A stable, ready-to-use mercurial diuretic.

Dose: From 0.5 to 2 cc. daily.

Supplied: In 2-cc. and 10-cc. ampoules.

Order a supply of 'Dicurin Procaine' Solution today from your local pharmacist. You will appreciate its effectiveness and ready-to-use convenience.



ELI LILLY AND COMPANY, INDIANAPOLIS 6, INDIANA, U.S.A:

The American Journal of Medicine

Vol. XVII

NOVEMBER, 1954

No. 5

Editorial

Enzymes and Templates in Bone Salt Formation

THE natural philosopher, in his contemplation of the processes of life, strives to resolve the activities of the living cell into the ultimate laws of physics and chemistry. The ancient schism between vitalist and mechanist has become more and more attenuated, and increasingly semantic, as the very border between inertness and life becomes progressively fine and intangible. Pale vestiges of the old contentions persist, however, although the lines of controversy have been redrawn. The question now is whether the innermost secrets of life can be presumed to reside in the chemical and physical obscurities of the intricate structure of the proteins, nucleic acids, carbohydrates and fats which make up the living tissue.

Apposite to all this, in a curious, distorted way, is the current discussion of the mechanisms of bone salt formation. Does elaboration of the bone salt require the agency of cellular activities or is it formed exclusively by the operation of physicochemical principles divorced from the living cell? The question is appropriate but should be divested of all vitalistic connotation. Cellular activities are being defined more and more inclusively by the manifold operation of enzyme systems, and enzymes are rapidly losing their mystic overlay. The current problem then is, not vitalism or mechanism, but enzymes or templates; and there is ample evidence that both participate.

The bone mineral, comprising approximately one-third of the total bone mass, is diffusely deposited in the osteoid matrix in the form of myriads of microcrystals which give the apatite lattice pattern upon x-ray diffraction and have the general composition of a hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$. These microcrystals are disposed in orderly orientation to correspond with

an intricate network of fibrils of collagen, a fibrous protein which forms the major component of the bone matrix. Diffusely interspersed among the fibrils is an "osseomucoid" ground substance which is composed of complex mucopolysaccharides including chondroitin sulfates; Glegg latterly has separated and, in part, identified some of the components chromatographically.

Until quite recently, the formation of the basic calcium phosphate bone salt was generally considered exclusively in physico-chemical terms of precipitation, in accordance with the laws of mass action. This view presumed saturation, with respect to calcium and/or phosphate, of the intercellular fluid, whether uniformly or localized at the site of bone formation by the action of the alkaline phosphatase of the osteoblast. The precipitation hypothesis based upon a simple ion

product is no longer tenable, for reasons ably summarized by Neuman and Neuman.¹

The Neumans indicate that basic calcium phosphate can form only by crystallization; either by stepwise addition of ions to a nucleation center or by a similar process involving the hydrolysis of secondary calcium phosphate, which has a K_{sp} conceivably within the possibilities of biologic systems. Such nucleation centers, it is suggested, act as templates for the further crystallization of the bone salt which thus ultimately infiltrates the whole of the conditioned matrix. The microcrystals of hydroxyapatite present an enormous surface, the site of ceaseless exchange, heteroionic as well as isoionic. This would account for the heterogeneity of bone composition and provides a mechanism for recrystallization.

¹ NEUMAN, W. F. and NEUMAN, M. W. The nature of the mineral phase of bone. *Chem. Rev.*, 53: 1, 1953.

While much of this scheme is based on sound evidence and rational implication, and is doubtless valid for the final phases of bone salt formation, there are difficulties. Not the least of these is in accounting for both initiation and termination of the crystallization process, which starts and stops independently in many different areas at different times. Morphologic evidence would seem to indicate quite clearly that this concept, in its present formulation, represents an oversimplification.

The central fact in the phenomenon of bone salt deposition is that it occurs selectively, only in certain predisposed tissues even though non-calcifying tissues also are bathed in intercellular fluid of the same composition. This implies that local as well as humoral factors are involved. It may be presumed that the local factors reflect specific cell activities involving the action of enzymes.

In apparent conflict with this deduction is the demonstration that bone mineral, properly aligned to collagen fibrils in relation to its *c*-axis, can be made to deposit *in vitro* in cartilage or bone matrix after treatment to destroy enzymes. This, however, requires exposure to calcium and phosphate in concentrations far exceeding physiologic limits, and presumably involves precipitation. It is doubtful that such experiments can be accepted as models of the naturally occurring phenomenon.

Little is known about the enzyme systems participating in bone salt formation.² Robison's bone alkaline phosphatase³ doubtless is involved

but precisely how has not been determined. Phosphorylative glycogenolysis has been shown to be a prerequisite to calcification of cartilage⁴ but the cycle has not been traced beyond phosphopyruvate formation; the disposition of the phosphoric and pyruvic acid moieties has not been established, nor has the fate of the high energy phosphate thus formed been settled. The changes in the matrix signalized by metachromasia and its subsequent disappearance remain obscure. The significance of the high content of citrate in bone has not been explained. Despite all these uncertainties, however, there can be little doubt that enzymes do play an important role in the formation of bone. They may well be concerned with the earlier phases of this complex process; in the preparation of matrix for "calcifiability," as well as in the delivery of high energy phosphate, appropriate sulfur compounds, and probably other elements as yet unrecognized.

Perhaps the most conspicuous lack in current theories of bone salt formation and dissolution, at least from the point of view of the pathogenesis of abnormalities of bone, is the failure to account for the action of a variety of vitamins and hormones. Deficiency or excess, notably of vitamins D, A and C, and of hormones derived from the parathyroid, adrenal and sex glands, profoundly affects the bone. There is no clue as to how these and other principles upset the steady state of the relationship between the mineral content of the bone and its components in the circumambient fluid. If analogy is permissible, it may be suspected that they operate here, as elsewhere, through the agency of enzymes.

ALEXANDER B. GUTMAN, M.D.

⁴ GUTMAN, A. B., WARRICK, F. B. and GUTMAN, E. B. Phosphorylative glycogenolysis and calcification in cartilage. *Science*, 95: 461, 1942.

² GUTMAN, A. B. and YÜ, T. F. A concept of the role of enzymes in endochondral calcification. Conf. Metabolic Interrelations, p. 167. New York, 1950. Macy Foundation.

⁸ Robison, R. The possible significance of hexosephosphoric esters in ossification. *Biochem. J.*, 17: 286, 1923.

The QRS Complex Deformity of Myocardial Infarction in the Human Subject*

ROBERT P. GRANT, M.D. and RAYMOND H. MURRAY, M.D. Bethesda, Maryland

ost present day methods for interpreting the clinical electrocardiogram use only a small part of the information contained in the tracing. The reason for this is that in these methods the diagnosis is usually based upon memorized deflection patterns seen in one or another lead, and there is no way to relate the information contained in one lead with that in the other leads or to use deflection contours which do not fall into one or another of the memorized categories.

This is well illustrated by the way in which the diagnosis of myocardial infarction is made from the QRS complexes of the clinical tracing. The electrocardiographic hallmark of infarction is, of course, the Q wave. However, it is not commonly realized that when an infarct produces Q waves in certain of the leads of a tracing it has also deformed the initial part of the QRS complexes in all other leads of the tracing, indeed in all possible body surface leads. In pattern methods of interpretation these other abnormalities are not recognized, and unless a Q wave is present the diagnosis of infarction may be overlooked. Furthermore, the Q wave produced by infarction is a deformity of only the first part of the QRS complex. Whether or not later parts of the QRS complex are also diagnostically altered is not known, for this part of the complex is not used in making the diagnosis of infarction by these methods.

However, the electrocardiographic deflection is more than simply a wave form pattern. It is an accurate measurement of the variations in electrical potential at the body surface, with each lead of the clinical tracing measuring this potential from a different point of vantage on the surface of the electrical field. The interpretation could be made much more accurately and confidently were there some way to treat deflections

as measurements of potential of a single electrical field, to integrate the information contained in all the leads, and to express it in some simple, rational, quantitative form. For many years the principles of vector analysis have been used in physics and electrical engineering to integrate measurements of potential from several points in an electrical system. By applying certain of these principles to the leads of the clinical electrocardiogram it is possible to convert the information contained in all twelve leads to a single quantitative form describing the distribution of potential on the surface of the body. Since the method uses the information in all leads, encompassing all possible variations in wave form which may occur in each lead, it is a more comprehensive and detailed method of interpretation than the pattern method. In addition, its quantitative aspects make the interpretation more objective and more accurate.

The QRS complex deformity produced by myocardial infarction is one of the most important problems in clinical electrocardiography. There are two aspects of this problem which can be clarified by the use of vector methods. First, what is the distribution of body surface potential which accounts for the various types and distributions of Q waves in the conventional leads in this syndrome, and can more objective criteria for evaluating Q waves be developed from this information? Second, recognizing that the Q wave is a deformity of only the first part of the QRS complex, is the duration of this deformed portion the same in all cases, and are there any other parts of the QRS complex which undergo characteristic alterations following infarction?

I. VECTOR PRINCIPLES EMPLOYED

The use of vector methods to interpret the routine clinical tracing is only one application of

^{*} From the Laboratory of General Medicine and Experimental Therapeutics, The National Heart Institute, Bethesda,

vector methods to electrocardiography. Another application is the recording of QRS and T "loops" or vectorcardiograms on the surface of a cathode tube oscilloscope, using special electrode locations and circuits. This application is of less direct clinical usefulness but has received considerably more attention in medical literature. For that reason it is important to point out that the two technics have certain conceptual differences which have a bearing on their clinical application. The oscilloscopic method is an attempt to produce a record of the electrical sequences taking place in the heart, expressing them in terms of instantaneous resultant electrical forces generated by the heart. On the other hand, the application of vector methods to the routine tracing is simply a technic for schematizing and systematizing the characteristics of the electrical field as it is manifested at the body surface; its purpose is to provide a method for gathering together the information contained in the various leads of the routine clinical tracing, and only secondarily and by inference and conjecture does it shed light on basic electrical sequences within the heart.

This difference is important because, in view of the eccentricity of the position of the heart in the chest and the characteristics of the body as a bounded conductor, one may question the accuracy with which the electrical forces generated within the heart can be defined from body surface electrodes, no matter what type of instrument is used for recording them. On the other hand, there can be no question as to the validity of using vector methods to schematize the deflections obtained from a number of points on the body surface. Indeed, it is the only method available in physics for bringing together measurements of electrical forces obtained from various points on the surface of an electrical field.

When the routine tracing is looked at from this vector point of view, it resembles other quantitating tests used in clinical medicine such as the glucose tolerance test, bromsulphalein excretion test, etc. In effect, in these tests precise measurements are made from a series of rather crudely obtained samples, and a graph is constructed from the measurements which gives in quantitative form a greatly simplified but useful picture of a complicated underlying phenomenon. From the vector point of view the routine clinical electrocardiogram also consists of a series of rather crudely obtained "samples." In

this situation they are "sampling" electrical potential from twelve different points on the surface of the electrical field. Precise measurements are then made from these samples and a "graph" is constructed which gives a quantitative but greatly simplified picture of the distribution of potential on the body surface. The graph in this case is the vector, an arrow which in its direction indicates the direction of a single electrical force which could account for the recorded characteristics of the deflection in each of the leads. That this vector might also be an accurate representation of a resultant electrical force generated by the heart is a possible and useful inference but is by no means a necessary conclusion before the method can be considered a valid technic for graphing the information contained in the deflections. It must be emphasized that as long as electrocardiography is at the mercy of body surface leads it can at best give only vague and generalized information regarding the electrical events which are actually taking place in the heart, no matter what methods are used for recording or interpreting the information.

The vector method used in this study is based upon the properties of the simplest type of electrical field: a directed electrical force or vector generated at the center of a cylindrical volume conductor. To understand the method one need only understand the way in which positive and negative deflections are distributed on the surface of this cylinder for a given vector direction, for the same principles govern to a large extent the distribution of positive and negative electrocardiographic deflections on the body surface of the human subject.

If unipolar V leads are recorded from the surface of this ideal cylinder, each deflection will be a measurement of the projection of the vector on the axis of that lead. The axis of a unipolar lead is the hypothetical line extending from the location of the exploring electrode on the surface of the cylinder to the origin of the vector at the center of the cylinder. Whenever an electrode is placed at such a point on the surface of the cylinder that the axis of the lead is perpendicular to the direction of the vector, it will record an isoelectric or zero deflection. There are a number of points on the surface of the cylinder where such zero deflections will be recorded. Since they lie on axes which are perpendicular to the vector, they form a pathway around the chest, in effect the pathway where a plane perpendicular to the

vector intersects the surface of the cylinder. This pathway is called by physicists the "null contour" for that vector and is illustrated in Figure 1. At all points on one side of the null contour the unipolar leads will record positive or upright deflections for that vector. This is the side toward which the vector points and it is called the "area of relative positivity" for that vector. At all points on the other side of the null contour unipolar leads will record negative or downward deflections. This is the region away from which the vector is pointing and it is called the "area of relative negativity" for that vector. The deflections, whether positive or negative, tend to become smaller the nearer the electrode lies to the null contour. The null contour and therefore the distribution of positive, negative and null deflections will, of course, be different for different directions of the vector. It can be seen from this that if one can identify a null contour one can plot the direction of the vector, for it must be relatively perpendicular to the plane defined by the null contour.

This then is the way in which positive, negative and null deflections are distributed on the surface of a cylindrical volume conductor when there is a single electrical force generated at its center. The chest of the human subject is more or less cylindrical. It follows from this that, regardless of the homogenity of the tissues of the body and regardless of the position of the heart in the chest, if the QRS or T deflections recorded on the chest of a human subject have such distribution of positivity and negativity that a null contour can be plotted for them, the deflections can be considered to be recording the electrical field of the heart as if there were just a single electrical force being generated, and all body surface electrode positions are in effect recording from this same electrical force. When such a null contour can be defined a vector can be drawn perpendicular to the null plane. This is roughly the direction of an electrical force which could cause this distribution of positive and negative deflections on the chest. It so happens that in the vast majority of human subjects null contours can be readily plotted from the body surface QRS and T unipolar lead deflections. It has been shown earlier that this can be done for over-all or mean deflections, and the present study illustrates that null contours can also be plotted for certain discrete instants in the course of the QRS interval.

Thus it can be concluded that for all practical

clinical purposes the distribution of positive and negative QRS and T deflections in the human subject tends to resemble the distribution of positivity and negativity produced by single electrical forces at the center of a cylindrical volume conductor. To be sure, when null

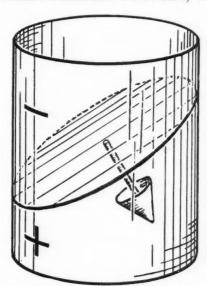


Fig. 1. A directed electrical force within a volume conductor, illustrating the distribution of the areas of relative electrical positivity and negativity for that force on the surface of the conductor. The two areas are separated by a region of relative null or zero electrical potential which lies on the pathway of intersection of a plane perpendicular to the electrical force at its origin. This pathway is called the null contour for that electrical force or vector.

contours are plotted on the chest of the human subject they often do not resemble perfectly the pathways of intersection of planes through the chest. Some of this is no doubt due to the fact that the body is not perfectly cylindrical in shape. It is also a reflection of the obvious fact that plotting null contours is a considerable simplification of the electrical events taking place in the heart. Nevertheless, it is remarkable that significant departures from ideal null contours are infrequent. An example of such a departure is seen in the so-called "isolated T wave negativity" syndrome, in which negative T waves are encountered in the area of relative positivity for the T vector. The clinical implications of this syndrome have been described elsewhere.1 Under certain circumstances components can also be detected in the QRS complex at precordial leads V₁ and V₂ which do not

conform with the distribution of the null contour for appropriate instantaneous QRS vectors.² Also, when the null contour of the mean T vector passes through the precordial region it will commonly show some departure in this region from a perfectly symmetric null contour. However, these examples of irregularities in the null contour are uncommon and they do not detract from the validity and usefulness of the vector method. They simply mean that under certain circumstances a schema that treats the body surface deflections as if they were all written by the same central vectors is too simple, and a more complex schema is necessary in these cases.

In summary, the vector constructions in this study are intended only secondarily to indicate the characteristics of electrical forces generated by the heart. Primarily they are intended simply to show the distribution of positivity and negativity on the body surface for a particular electrical event in the heart, for this explains the particular contours of the QRS complexes in each of the various leads of the clinical tracing. With this understanding of the relationship between deflection contours and the electrical field on the body surface the interpretation of Q waves and other wave forms becomes more rational and accurate than is possible by memorizing deflection patterns.

II. THE ELECTRICAL CHARACTERISTICS OF CURRENT QRS CRITERIA FOR THE DIAGNOSIS OF MYOCARDIAL INFARCTION

A number of different schemas have been described for localizing infarcts from the distribution of Q waves in the clinical tracing by assuming that the electrodes writing abnormal Q waves overlie the infarcted region of the heart. However, there are two aspects of this which should be pointed out. First, the Q wave is an electrical finding, and the electrical effects of infarction are not necessarily identical in size and location in the heart with its histologic effects. Furthermore, as will be shown in the second part of this study, there are other factors besides the location of the infarct that determine which leads will show Q waves. Second, a Q wave of .04 second's duration which, as will be seen, is the duration a Q wave must have to be diagnostic of infarction, is recorded when the electrode is placed on the region of the chest which is electrically negative for the first .04 second of the QRS interval. The twelve leads of

the clinical tracing sample only a selected portion of the chest surface, and whether or not one of these electrode locations will lie in the area which is electrically negative for the first .04 second in a given case will depend upon the arbitrariness of these electrode locations and, often, the slightest of variations in direction of the electrical forces during the first .04 second of the QRS interval. The most rational way to evaluate the meaning and adequacy of present day Q wave criteria for the diagnosis of infarction would be to study the distribution of positivity and negativity on the chest surface during the first .04 second of the QRS interval in a number of normal subjects and to compare this with the distribution in subjects with Q waves in the routine tracing which conform with current criteria for the diagnosis of infarction. That is the purpose of the first part of this study.

Methods. The most accurate method for plotting null contours is to record unipolar deflections from all regions of the chest, identify the electrode locations where null or transitional deflections are written, and the line through these points defines the null contour for that electrical event. In 115 subjects over forty chest leads were recorded from the anterior, lateral and sometimes posterior surfaces of the chest in order to plot null contours for several instants during the QRS interval. Seventy-seven of these subjects had Q waves in the routine tracing diagnostic of infarction and thirty-eight subjects had no such Q waves, by current criteria. The deflections were obtained at 2 inch intervals along a series of vertical lines on the chest using a single channel Viso-cardiette electrocardiograph, and were mounted in the same geometric arrangement in which they had been obtained. Null contours were plotted from the tracings and spatial vectors drawn for three instants during the first part of the QRS cycle, roughly, .01 second, .02 second and .04 second. For the null contour at .01 second the deflections along each line were examined for the electrode location where the initial take-off of the QRS deflection changed from being positive at one electrode location to negative at the next or vice versa. A line was drawn through these electrode locations which indicated the null contour for the very first instant in the QRS interval, and a vector was drawn perpendicular to the plane defined by the null contour. This is called the .01 second vector. The null contour at .02 second was plotted by finding the electrode locations

AMERICAN JOURNAL OF MEDICINE

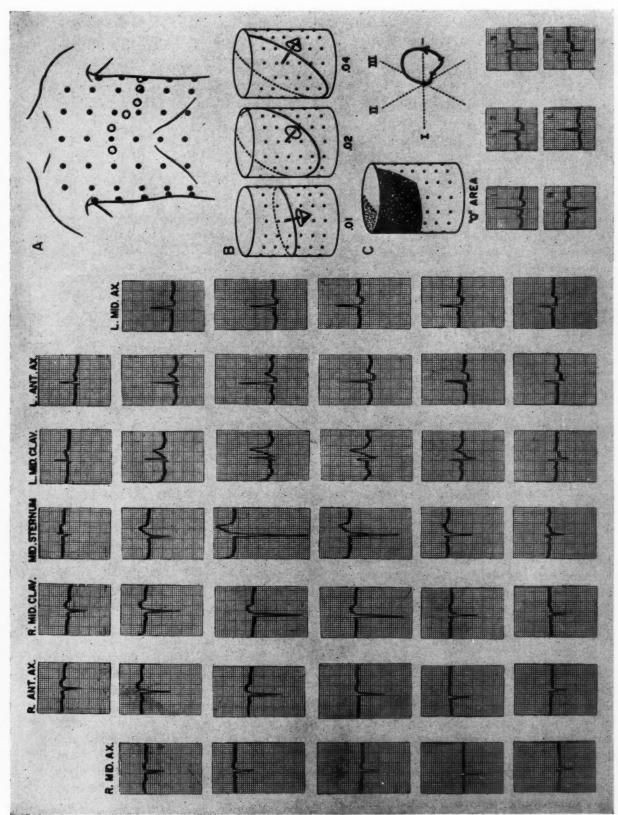


Fig. 2. Illustrating the null contour method for determining the directions of instantaneous QRS vectors. The unipolar lead deflections on the left were obtained from electrode locations indicated by black dots in (A). Conventional precordial electrode locations are indicated by circles in the figure. B, three instantaneous QRS vectors plotted from the deflections. C, the Q area and the frontal plane projection of the QRS loop. Unipolar and bipolar limb leads from this patient are shown in the lower right corner. The QRS loop is marked at .02 and .04 seconds.

where the QRS deflection was isoelectric at .02 second (one-half of the smallest time interval in the tracing); and the null contour for the instantaneous vector at .04 second was plotted by finding the electrode locations where the QRS complex was isoelectric at .04 second.

The technic for plotting null contours is shown in Figure 2. The unipolar lead deflections obtained from the anterior and lateral chest of a typical subject are shown. A cylindrical reference figure is used for plotting the null contours and the relative locations of the multiple chest leads are shown by black dots on each cylinder. The vectors are drawn as if they originated at the center of each null plane. This is done for convenience for no satisfactory method has yet been devised for calculating the actual effective origin of a resultant electrical force of the heart in the human subject. Null contour plots for approximately .01, .02 and .04 second are shown in this figure.

It can be seen that the null contour at each of the instants studied divides the body surface in half. One-half of the chest surface is an area of positivity while the other half is an area of negativity. The region of the chest which is electrically negative for the entire first .04 second of the QRS interval can be plotted by superimposing the null contours for the three instants, as shown in Figure 2C. V leads recorded from any point within this region will write Q waves of .04 second's duration. This is called the "Q area" and is a useful calculation because it summarizes the early QRS vectors and at the same time relates them to the distribution of Q waves on the chest, which have such importance in clinical electrocardiography. The interval of .04 second was selected for the Q area determinations because, as will be shown, myocardial infarction alters at least the first .04 second of the QRS interval in the majority of

Frontal plane projections of the QRS "loop" are also shown in the illustrations. These were constructed from the contours of the QRS complexes in the unipolar and bipolar limb leads in each case by the method described earlier. The "loops" are marked at .02 and .04 second to help in comparing the directions of the instantaneous vectors plotted from the null contours with their directions as manifested in the limb leads. The conventional limb and precordial leads for each case are also shown in order to assist in relating the vector information

to the contours of the QRS complexes in the conventional leads. It should be pointed out that these studies are entirely electrocardiographic, and no pathologic or clinical correlations were attempted.

Normal Subjects. Thirty-eight subjects with normal QRS interval duration and no QRS complex abnormalities of myocardial infarction by current Q wave criteria were studied by this method. In all cases the Q area lay on the right side of the chest. However, its particular location on the right chest varied markedly, as illustrated by Cases 8, 95 and 113 of Figure 3. This variation proved to be due to the fact that the instantaneous vectors during the first .02 second of the QRS interval vary widely in direction among subjects with normal QRS electrical fields. At .01 second the vector may have any direction through 360 degrees in the frontal plane and is anteriorly directed. At .02 second it may have any direction through 180 degrees, pointing leftward and anteriorly. On the other hand, at .04 second the vector varies within only 90 degrees in direction among normal subjects and is always pointing leftward, inferiorly and slightly posteriorly, relatively parallel with the direction of the mean spatial QRS vector for that subject. It is because the vector at .04 second is leftward in direction that the Q area always lies predominantly on the right side of the chest in the normal subject.

Seventy-seven cases with Q waves in the conventional leads conforming with current criteria for the diagnosis of myocardial infarction were studied by this method. In all cases the Q area occupied large portions of the left side of the chest. However, the particular region of the left chest where the Q area lay varied widely from case to case and therefore they were grouped into five types. The five types have been given anatomic names in this study resembling those used in clinical electrocardiography for designating the location of infarctions. However, it is well to remember that these names only indicate the location of the Q area on the chest surface and do not necessarily indicate the region of the heart that has been infarcted.

Strictly Anterior Q Area. There are twenty-six cases with a Q area on the anterior surface of the chest, indicating that the average direction of QRS vectors during the first .04 second was directly posterior. In these cases the conventional clinical tracings showed Q waves at V_1 and V_2 and occasionally V_3 but no Q waves of

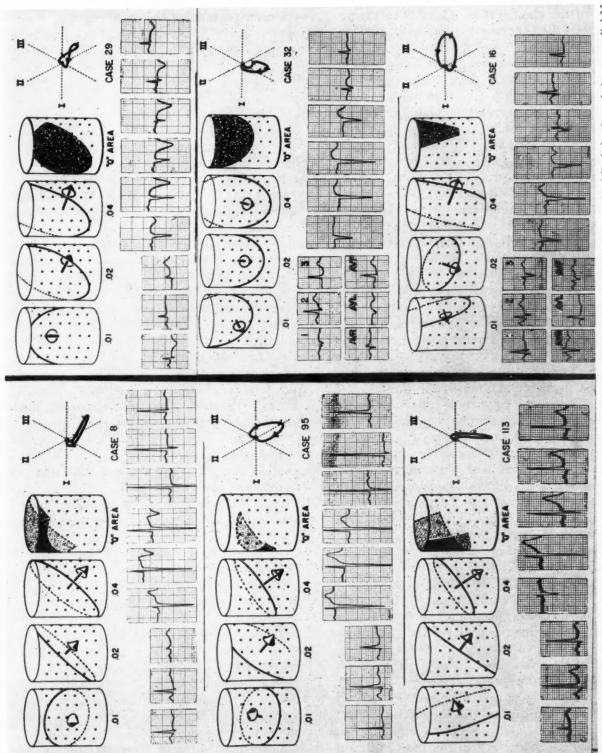


Fig. 3. Instantaneous QRS vectors, Q area and frontal plane QRS loop for six subjects; the three standard limb leads and six precordial V leads are shown beneath the vector plots for each case.

more than .02 second's duration in any of the limb leads. Although relatively few of the precordial leads showed Q waves, the Q area was usually quite large, often including as much as a third of the chest surface. Case 29 in Figure 3 illustrates the Q area in this group of cases.

Anterolateral Q Area. In sixteen cases the Q area lay on a more anterolateral region of the chest, indicating that the average direction of the QRS vectors during the first .04 second of the QRS interval was more rightward than in the strictly anterior group of cases. The clinical tracings in these cases showed Q waves of .04 second among more lateral precordial leads as well as in leads 1 or aVL or both.

In six cases in this group the Q area was quite small. These are the cases in which Q waves were seen in the clinical tracing in only one or two of the more lateral precordial leads, often with no O waves of .04 second's duration in any of the limb leads, as illustrated by Case 16 of Figure 3. The remaining cases of this group had quite large Q areas, as illustrated by Case 32 of this figure. The difference between the two types of anterolateral Q area is related to the direction of the vector late during the first .04 second. In the small Q area cases this vector was more nearly normal in direction than in the large Q area cases. The infarct appeared to have influenced the vector direction during only the first .02 to .03 second in the small Q area cases, while it deformed the first .04 second or more in the large Q area cases. This does not necessarily mean that the infarct was anatomically larger in the large Q area cases, for the degree of deformity of QRS forces is not known to be related to the size of the infarct. In some cases the small Q area probably represents a healing stage of a large Q area infarct, with the vector at .04 second being the first to return toward normal.

Inferior or Diaphragmatic Q Area. In eighteen cases the Q area occupied the inferior part of the chest. The average direction of the QRS vector during the first .04 second of the QRS interval in these cases was superior, as if pointing away from the diaphragmatic region of the heart. Q waves of .04 second were seen in leads III, aVF and often in lead II in the clinical tracing. Although this "Q3" pattern of infarction has been called "posterior" in the past, both anatomic and electrical evidence indicate that the infarct lies on the diaphragmatic surface of the heart and not its posterior surface in most of these cases.³

In all cases the Q area involved the lower chest and trunk. In eight cases it extended further up the chest posteriorly than it did anteriorly, suggesting that the electrical lesion included the posterior portions of the diaphragmatic surface of the heart. Under these circumstances the early QRS vectors point anteriorly as well as superiorly. This causes the initial R waves at V_1 and V_2 to be abnormally broad and tall, as exemplified by Case 44 of Figure 4.

On the other hand, in five cases the Q area extended further up the chest anteriorly than it did posteriorly, often extending high enough to include the precordial region and produce Q waves in certain of the precordial leads, suggesting that the lesion may have involved more anterior regions of the diaphragmatic surface of the heart. This is illustrated by Case 108 in Figure 4. In the past the combination of Q waves on lead III plus Q waves in the precordial leads has often been interpreted to mean that the patient has both a "posterior" and an "anterior" infarction. Although this may be the case anatomically, it is not true electrically. The QRS complex is the summed record of electrical activity in all parts of the heart at each instant; and if more than one infarct is present, the body surface QRS complex will be a summed record of the electrical effects of them all. The proof of this lies in the fact that there is only one Q area in any subject. Q waves will be written in both limb and precordial leads whenever the Q area has such a location that certain of the limb lead and precordial lead electrodes both lie within it.

Strictly Posterior Q Area. In seven cases the Q area lay on the posterior surface of the chest. This indicated that the average direction of the QRS vectors during the first .04 second of the QRS interval was anterior, producing diagnostically tall, broad R waves at V₁ and V₂. The Q area was quite large and tended to lie more on the left than on the right side of the chest posteriorly. This somewhat rightward direction of the early QRS vectors produced Q waves of .02 second or more on lead 1 or aVL or both. That R waves exceeding .04 second in duration at V₁ and V₂ may be diagnostic of infarction has been described before; however the syndrome is not widely recognized.^{4,5}

Since the Q area of posterior infarction lies somewhat eccentrically on the back, it may encroach on the electrode position for one or another of the conventional leads and in this way produce Q waves of .04 second's duration in

AMERICAN JOURNAL OF MEDICINE

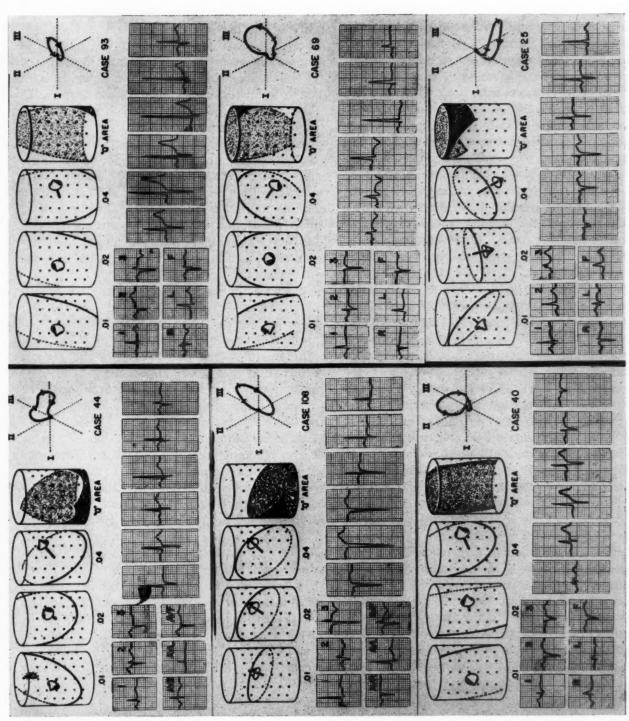


Fig. 4. Tracings and vector plots in six cases. The limb leads are mounted on the left, with the standard bipolar leads above and unipolar limb leads below as indicated.

one or more leads of the clinical tracing. For example, in Case 93 of Figure 4 the Q area surrounds the chest inferiorly. This means that the vectors during the first .04 second are directed somewhat superiorly in addition to anteriorly, and accordingly there are Q waves of .04 second in leads II, III and a VF which is the pattern of diaphragmatic infarction. In Case 69, on the other hand, a Q wave of .04 second is seen in lead aVL. This has often been considered the pattern of high lateral infarction. However, the Q area is principally posterior in location, and only because the initial vectors are pointing slightly rightward does the Q area include the left shoulder and a Q wave appear in lead aVL. By contrast, in Case 40 none of the electrodes for the conventional tracing lie in the Q area and no Q waves of .04 second are to be seen in any of the leads. However, the broad R waves of over .04 second's duration at V1 and V2 reflect an abnormal posterior location of the Q area diagnostic of infarction.

It should be pointed out that R waves of .04 second's duration may be seen at V₁ and V₂ in normal subject. The reason for this is that R waves of .04 second's duration will be recorded from the region of the chest diametrically opposite to the region where Q waves of .04 second are recorded. Thus whenever the Q area extends onto the left chest posteriorly in the normal subject, as in Case 95 of Figure 3, R waves of this duration may be written in certain of the precordial leads. The posterior Q area of the normal subject is always smaller than the posterior Q area due to infarction. The reason for this is that in the normal subject the instantaneous vector at .04 second is normally directed, that is, it is parallel with the mean QRS vector for that subject which is directed leftward and inferiorly. Therefore in the normal subject with a posterior Q area the instantaneous vector during the first .04 second must change direction through 180 degrees. This will cause the Q area to be small. On the other hand, in the subject with a posterior Q area of infarction the vectors throughout the first .04 second will all point anteriorly and there is little change in their direction. Therefore the Q area will be quite large, including as much as a third of the chest surface in these subjects.

High Lateral Q Area. In ten cases the Q area occupied the superior or high left lateral part of the chest. In all cases the left shoulder was included in the Q area and therefore all cases

showed Q waves of .04 second in Lead aVL of the conventional tracing. In three cases the O area symmetrically included both shoulders and lead aVR also showed a Q wave of .04 second's duration in these cases. It will be noted in Case 25 of Figure 4 that had the Q area extended only a few centimeters lower on the anterior chest it would have included the precordial region and leads V1 and V2 would have shown Q waves. The splintering of the R waves from V₁ to V₂ in this case indicates how near the Q area is to these precordial electrodes. The slight difference between the Q area of high lateral infarction and that of strictly anterior infarction is often due to only slight difference in the direction of the vector at .01 or .02 second. It is probable that certain of the cases called high lateral infarction represent healing stages of strictly anterior infarction because the early QRS vectors are more nearly normal in direction in these cases than in the cases of strictly anterior infarction.

Summary. Everyone, whether normal or abnormal, has a Q area. That is, in every subject there is a region of the chest where Q waves of .04 second's duration can be recorded. The only difference between the Q area of the normal subject and that of the subject with myocardial infarction is in its location. This must be borne in mind whenever deflections are recorded from non-conventional regions of the chest when looking for "infarct Q waves," as has frequently been recommended in electrocardiographic literature. Occasionally, normal Q waves will be recorded when this is done and there is no way to differentiate these deflections from those of infarction from the wave contour alone.

The distribution of the Q area in the normal subject has not been extensively studied. Nevertheless, the difference in location of the Q area between the normal subjects and the subjects with infarction studied in this series of cases can be described in terms of the direction of the average or mean QRS vector during the first .04 second of the QRS interval (the mean .04 vector). When this vector is directed more than 45 degrees away from or is directed posteriorly to the mean spatial QRS vector in a patient with normal QRS duration, the QRS electrical field is abnormal and infarction is the likeliest cause. This is a much more precise and objective definition of the QRS deformity of infarction than that based upon the distribution of Q waves in the various leads of the clinical tracing. Another

way of expressing this is in terms of the approximate lie of the left ventricle (Figure 10A): When the mean .04 vector is directed away from a region of the left ventricular myocardium, QRS deformity of infarction is present; but when it is directed away from the location of the mitral-aortic orifice of the left ventricle, the QRS electrical field is normal.

It has long been considered that Q waves of infarction are recorded from electrode locations which overlie the location of the infarct in the left ventricle. In a general way this may be true, for the Q area of infarction tends to lie on the left side of the chest while the Q area of the normal subject tends to lie on the right side of the chest. However, as can be seen in the illustrations, there are many normal subjects with Q areas that extend into the left side of the chest, especially posteriorly, and in these subjects Q waves may be recorded from regions of the chest overlying the left ventricle. Likewise, in most cases of infarction the Q area extends to a greater or lesser extent into the right chest. If one considers the location of the center of the Q area, this formulation becomes more valid. For example, with reference to Figure 10A, a plane passing through the mitral-aortic orifice of the left ventricle will intersect the surface of the body to the left of the neck superiorly, to the right of the umbilicus inferiorly; the intersection will pass along the right side of the chest surface anteriorly and along the left side of the chest posteriorly. The present studies indicate that when the center of the Q area lies to the left of this line infarction is present regardless of the distribution of individual Q waves; when it lies to the right of this line the QRS field must be considered normal, as far as present day criteria and methods of recording are concerned.

It is apparent, in any case, that the QRS electrical field abnormality represented by the Q wave criteria currently used for diagnosis of myocardial infarction is in most instances objectively and strikingly different from the QRS electrical field of the normal subject. This means that these Q wave criteria probably rarely lead to a false positive diagnosis of myocardial infarction. However, there are certain types of infarction which these criteria will tend to miss. The reason for the failures is partly related to the particular body points which are used for electrode locations for the conventional clinical leads. These locations, especially the precordial lead locations, were selected more or less

empirically in the past, and it is necessary that the Q area of infarction actually invade the location of one or more of these electrode positions before Q waves of diagnostic duration will be seen in the clinical tracing. There are at least two abnormal Q areas which occupy regions of the chest where no electrodes for the conventional ECG are placed, and these two Q areas are therefore unaccompanied by any diagnostic Q waves in the routine tracing. These are the superior and the strictly posterior Q areas. The mechanism and type of QRS deformity which these two sites of infarction will produce have already been discussed.

At present the easiest and most rational way to decide whether a Q wave of .03 to .04 second's duration in a given lead is normal or abnormal is to study the distribution of the Q area for that subject. In most cases this can be done from the conventional clinical tracing by plotting null contours for two or three instants during the first .04 second of the QRS interval. If this proves to be difficult or inconclusive, V leads may be recorded in a systematic manner from the chest surface, as was done in these cases, and the Q area plotted from the deflections. This is the most accurate method yet devised for studying the body surface electrocardiogram in the human subject. In future clinical-electrocardiographic-pathologic correlation studies, the use of vector methods such as these will unquestionably lead to greater accuracy in electrocardiographic recognition of myocardial infarction.

III. A CONTROLLED STUDY OF THE QRS COMPLEX DEFORMITY PRODUCED BY MYOCARDIAL INFARCTION

The most accurate way to study the effects of infarction on the QRS electrical field is to compare postinfarction and preinfarction tracings in the same patient. To this end 190 cases of infarction with one or more satisfactory tracings within one year prior to their first postinfarction tracing were collected.* Multiple precordial

^{*} We wish to thank the following cardiologists for permitting us access to their electrocardiographic files: Dr. William Milnor, Johns Hopkins Hospital; Dr. Edward Orgain, Duke University Hospital; Dr. John Evans, George Washington University Hospital; Dr. Nathan Bloom, Medical College of Va.; Dr. Heinz Magendantz, New England Medical Center; Dr. Charles Kossman, Bellevue and Lennox Hill Hospitals; Dr. Reno Porter, McGuire Veteran's Hospital; Col. Thomas Mattingly, Walter Reed Hospital; Dr. Robert Whipple, Naval

V leads in addition to the conventional limb leads had been recorded in all cases. Cases with QRS prolongation beyond .12 second in either the preinfarction or postinfarction tracing were not included in the series.

Vector methods of analysis were used to compare pre- and postinfarction tracings in each case. This is the most accurate method at present available for comparing two multiple lead electrocardiograms. The vector method used is the null contour method described, adapted to the twelve body surface leads of the clinical electrocardiogram. Because only twelve leads are recorded and because one cannot be certain that identical electrode locations were used for each tracing in a given patient, the vector calculations are necessarily much less accurate than in the earlier study. In brief, the method depends upon using the characteristics of the QRS complexes in the limb leads to determine the direction of the vector as projected on the frontal plane of the body. Then, the extent to which the vector is directed anteriorly or posteriorly to this frontal plane projection is determined by identifying the precordial lead electrode location where the transitional or isoelectric form of the deflection is written, for this electrode location lies on the null contour for that vector.1 Mean and instantaneous spatial QRS vectors, Q areas and QRS loops were calculated for both the pre- and postinfarction tracings for each case, just as in the earlier study.

All but three of the 190 cases fell into one or another of three groups using the criteria described: (1) fifty-one cases of strictly anterior infarction, (2) thirty-seven cases of anterolateral or high lateral infarction, and (3) ninety-nine cases of diaphragmatic or inferior infarction. The remaining three cases were examples of strictly posterior infarction; however, only a single preinfarction tracing was available in each of these cases and therefore they are not included in the present study.

It is important to realize that the cases were collected by searching among tracings which showed ECG changes identified as due to infarction by the clinical staff of each of the institutions visited. To this extent the series is limited to cases which showed QRS and ST-T changes diagnostic of infarction by current widely

Medical Center; Dr. Ernst Simonson, Veterans' Hospital, Minneapolis, Minn.; Dr. T. J. Perin, Mount Alto Veterans' Hospital; Dr. Joseph Vander Veer, The Pennsylvania Hospital. accepted criteria. No attempt was made to correlate the clinical or pathologic features with the ECG findings in these cases.

RESULTS

1. The Portion of the QRS Interval That Is Involved by Myocardial Infarction. When the directions of the instantaneous vectors in pre- and postinfarction tracings were compared in these cases, it was found that eleven cases showed deformity of less than the first .04 second of the QRS interval, while all the remaining cases (95 per cent of the entire series) showed deformity of the first .04 second or more of the QRS interval. Thus, in the overwhelming majority of cases the first .04 second of the QRS interval was deformed. This tends to confirm the empiric clinical criterion that an abnormal Q wave in a given lead must be .04 second in duration before it can be considered diagnostic of infarction.

It is of interest that ten of the eleven cases with deformity of less than .04 second were in the strictly anterior group of cases, while those with deformity exceeding .04 second were principally in the diaphragmatic group of cases. This is probably due to the characteristics of precordial QRS complexes rather than to a difference in the nature of the electrical lesion. Normally the initial R waves at V1 and V2 usually have a duration of only .02 second. Therefore the directions of the early QRS forces need be abnormal for only the first .02 second in order to produce Q waves of .04 second's duration diagnostic of infarction in these leads. On the other hand, the QRS complexes in leads III and aVF are usually positive for the later portions of the first .04 second and therefore the instantaneous QRS vectors must be abnormal in direction for the entire .04 second or more in order to produce Q waves diagnostic of infarction in these leads.

These points are illustrated in the following two cases: Case AS-7 in Figure 5 is an example of strictly anterior infarction with deformity of QRS forces for only the first .02 second of the QRS interval. Incidentally, it will be noted that in the postinfarction tracing there is a tiny Q wave in lead 1, initial R waves at V₂ and V₃ and a Q wave at V₃. This is ordinarily considered to be the QRS pattern of anterolateral infarction. However, it can be seen by comparing the preand postinfarction null contour diagrams that the only effect of the infarction has been to cause the .01 and .02 second vectors to rotate posteriorly. Therefore the electrical lesion was strictly

AMERICAN JOURNAL OF MEDICINE

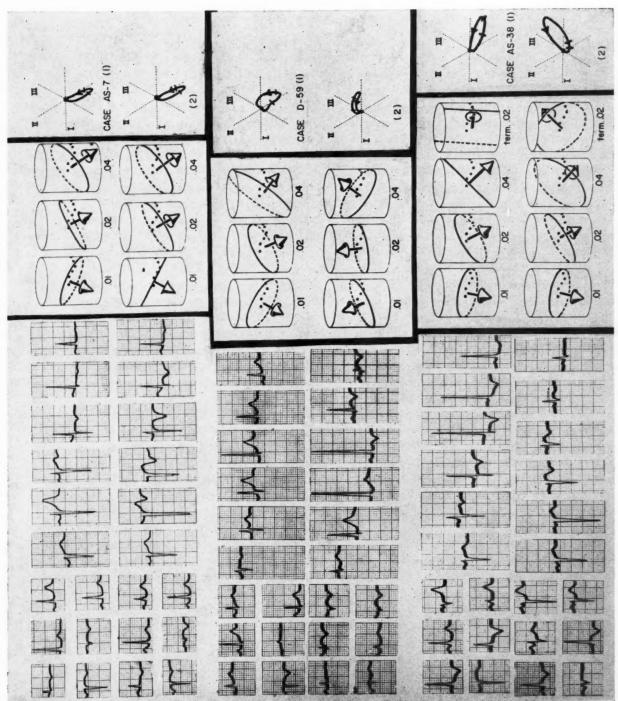


Fig. 5. Comparison of the pre- and postinfarction tracings in three cases. The preinfarction tracings with vector plots are shown above and the postinfarction tracings and vector plots below in each case. The limb leads are mounted on the left with the standard bipolar leads above and unipolar limb leads below as in the previous figure.

anterior in location. The effect on the conventional leads looks like an anterolateral infarction because the posterior rotation is not very great and the vector at .01 second was already rightward in the preinfarction tracing. Case D-59 in the same figure demonstrates deformity of more than .04 second's duration, with only the last .02 second of the QRS interval remaining unchanged. This is best seen by comparing the pre- and postinfarction frontal plane QRS loops. It will be noted in this case that the R waves at V₁ and V₂ have become prolonged as a result of infarction. This is due to the anterior direction of the vectors during the first .04 second of the QRS interval, and indicates that the infarct has a somewhat posterior as well as diaphragmatic electrical location. As was mentioned earlier, these broad R waves are as diagnostic of infarction in these leads as are Q waves of this duration in other leads.

Occasionally, the QRS complexes are deformed by anterior infarction without producing Q waves on any of the leads of the conventional tracing. Case AS-38 in Figure 5 is an example of this. There is no question but that the QRS complexes are altered in the postinfarction tracing but no Q waves of .04 second are to be seen in the routine tracing. Nevertheless, the Q area is near the location of the precordial leads, and there is a diagnostic abnormality present for, as can be seen in the drawing of the postinfarction QRS loop, the angle between the mean .04 vector and the mean spatial QRS vector is considerably in excess of 45 degrees. The principal alteration of the early vectors in this case has been the posterior rotation they have been caused to take. This posterior rotation is not as great as in the usual case in anterior infarction and that is why no Q waves are seen in the precordial leads.

Are early QRS forces ever spared and only later forces deformed by infarction? The answer to this question was sought in a special group of cases. It has long been recognized that occasionally infarction will produce marked and characteristic alterations in the ST and T waves but no diagnostic Q waves. It was hoped that careful comparison of pre- and postinfarction tracings in such cases might disclose in certain of them unchanged initial QRS vectors but significant alterations in later QRS vectors with no prolongation of the QRS interval. Seventeen such cases have been studied; and although this is a small number of cases, careful analysis failed to show significant change in either direction or

magnitude of the QRS instantaneous vectors in any of them. In short, no cases were encountered in the present study in which QRS vectors were altered by infarction without alteration of the very first vectors of the QRS cycle.

2. Alterations in the Terminal Vectors of the QRS Interval by Myocardial Infarction. Perhaps the most important and certainly the most unexpected finding in this study was the frequency with which all forces of the QRS interval were altered by infarction without significant prolongation of the QRS interval. In over a third of the cases in this series the terminal vectors of the QRS cycle were altered in addition to the early vectors. The terminal vector alteration was quite different from the initial vector alteration and also varied markedly with the electrical location of the infarct.

Strictly anterior: Terminal vector alteration was infrequent in the strictly anterior group of cases, occurring in only eight of the fifty-one cases in this group. In two of the eight cases the QRS interval was prolonged from .08 second to .10 second and in the remaining six there was no measurable prolongation of the QRS interval. In all eight cases the terminal vector was caused to point superiorly and rightward in the frontal plane so that S waves appeared in all three limb leads. In three of the eight cases the terminal vector also pointed slightly anteriorly so that there was a terminal R' in V1 and V2 producing a QRS pattern in the conventional leads which was indistinguishable from what has been called the S₁S₂S₃ pattern. This was the only type of terminal vector alteration seen in the strictly anterior infarct cases, and case AS-54 in Figure 6 illustrates it. This S₁S₂S₃ type of terminal vector change was also seen in four of the diaphragmatic infarction cases and in one case of anterolateral infarction, indicating that its occurrence is unrelated to the location of the infarct.

It is of interest that in all twelve cases with this type of terminal vector alteration following infarction the terminal .02 vector was rightward in the preinfarction tracing, a direction which occurred in less than 15 per cent of the preinfarction tracings in the series as a whole. This suggests that there was perhaps some vulnerable variation in conductivity at the base of the septum or in the region of the crista supraventricularis of the right ventricle before the infarction took place. It was not due to a hemodynamic disturbance such as cor pulmonale, for the

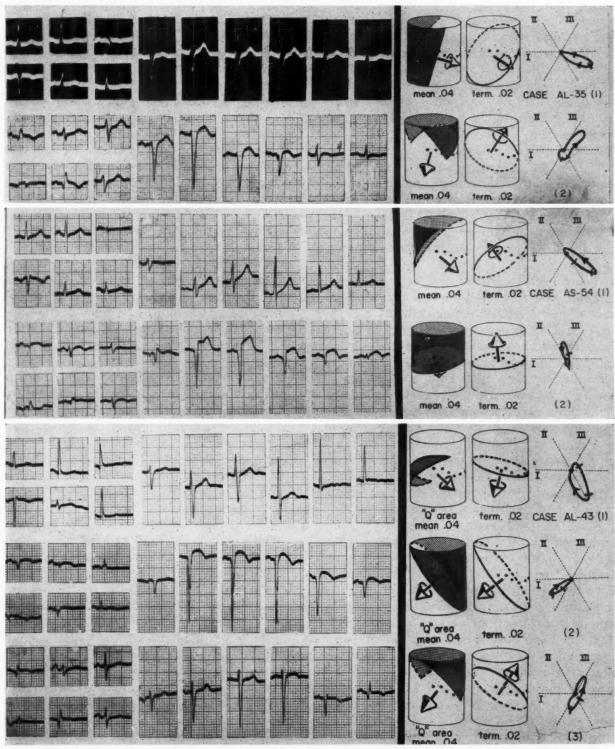


Fig. 6. Comparison of pre- and postinfarction tracings in three cases. Tracings mounted as in the previous figure. The Q area (shaded) and the mean direction of QRS vectors during the first .04 seconds of the QRS interval (the "mean .04 vector") are shown in the first cylindrical reference figure for each tracing. In the second cylindrical reference figure the direction of the vector for the last .02 seconds of the QRS interval is shown.

electrocardiographic defect did not disappear after the acute stages of the infarction subsided in any of the cases.

Anterolateral: Among thirty-seven cases of anterolateral infarction seventeen or nearly half of the cases showed alterations in direction of the terminal .02 vector when pre- and postinfarction tracings were compared. In six of these cases the QRS interval was prolonged by .02 second, and in the remaining eleven cases there was no measurable prolongation of the QRS interval. In all seventeen cases the terminal .02 vector pointed superiorly, leftward and posteriorly after infarction and was always directed slightly posteriorly to the electrical location of the infarct. Case AL-35 of Figure 6 illustrates this terminal vector alteration and it can be seen that the vector points posteriorly to the location of the Q area.

There were four cases in which as a strictly anterior infarction extended laterally it acquired this type of terminal vector defect. Case AS-9 in Figure 7 illustrates this. In the first postinfarction tracing the effects of strictly anterior infarction are present and it can be seen that the terminal part of the QRS complex is unchanged in any of the leads. However, in the second postinfarction tracing, taken three weeks later, the initial vectors are further changed in direction, now pointing rightward, as if away from a more lateral region of the heart. With this extension the terminal forces are for the first time altered in direction, pointing in the direction seen in other cases of anterolateral infarction.

Case AS-40 of Figure 7 illustrates another feature of the terminal vector alteration which follows infarction. In the first postinfarction tracing it can be seen that the initial vectors have been rotated rightward by the infarction, indicating that the electrical defect had an anterolateral location, and a terminal vector alteration has taken place which is similar to that seen in other cases of anterolateral infarction. However, in the second postinfarction tracing, taken three days later, the QRS complexes have become prolonged by .04 second, now measuring .12 second. The important feature here is that there has been little or no alteration in direction of either the early or terminal vectors in this tracing; the QRS complexes in the various leads are exactly the same in contour, showing only prolongation of the last part of each complex. If this prolongation were due to left bundle branch block, which it

superficially resembles, there should be a change in the direction of the initial forces of the QRS cycle, for the pathways of excitation during the first .04 second are altered by this type of block. On the other hand, if it were due to a block of more peripheral extensions of the conduction network, one would expect the terminal forces to be altered in direction in accordance with the altered sequences of late depolarization. Neither of these occurred. The only other explanation for this prolongation of terminal QRS forces with no change in their direction is to postulate either a slowing of conduction permeation or a greater persistence of depolarization as a membrane event in this last region of the heart to be activated. This type of QRS prolongation is not uncommon and is probably not restricted to myocardial infarction. It is frequently permanent and does not appear to be of serious clinical import in itself.

Diaphragmatic: Among the ninety-nine cases of diaphragmatic infarction, thirty-four or onethird of the cases showed terminal vector alterations. As mentioned earlier in four cases the S₁S₂S₃ type of terminal vector alteration was produced. In the remaining thirty cases the terminal vector was caused to point rightward, inferiorly and slightly posteriorly. In ten of the thirty cases the QRS interval was prolonged by .01 to .02 second and in the remainder no measurable prolongation of the QRS interval took place. Case DAL-8 in Figure 8 illustrates this terminal vector alteration in diaphragmatic

infarction.

The mechanism for the terminal vector alteration in myocardial infarction is not known. In 1950 First, Bayley and Bedford⁶ described a conduction defect following myocardial infarction in which, with the QRS interval prolonged beyond .12 second, the terminal vectors were relatively opposite in direction to the initial vectors. The authors termed this infarction pattern "peri-infarction block" and suggested that with a subendocardial location of the infarct the normal perpendicular spread of excitation from endocardium to the unifarcted epicardium overlying the infarct was prevented, and excitation could reach this region only by circuitous spread around the infarct with resultant delay of .04 second or more. In the present study the terminal vectors in the diaphragmatic and anterolateral cases were relatively opposite in direction to the initial QRS vectors. To this extent the concept of peri-infarction block may be a satisfactory explanation. However, unlike

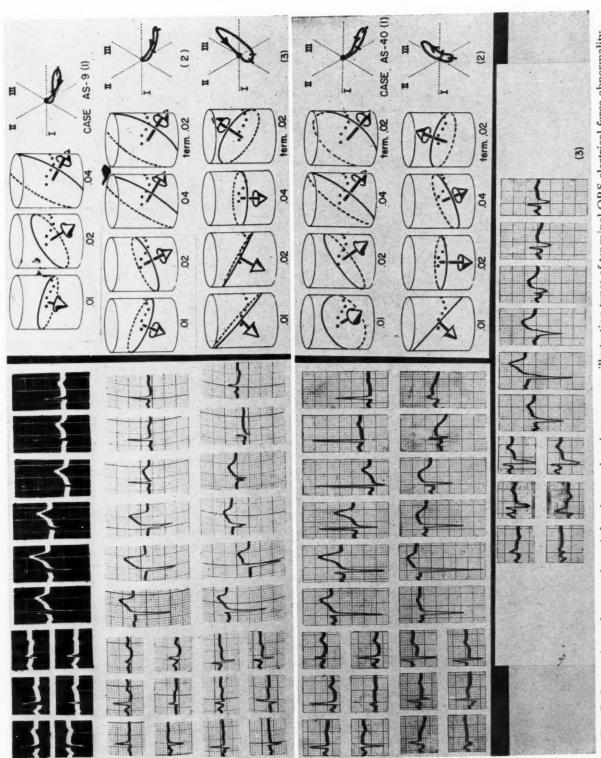


Fig. 7. Comparison of pre- and postinfarction tracings in two cases, illustrating types of ter minal QRS electrical force abnormality.

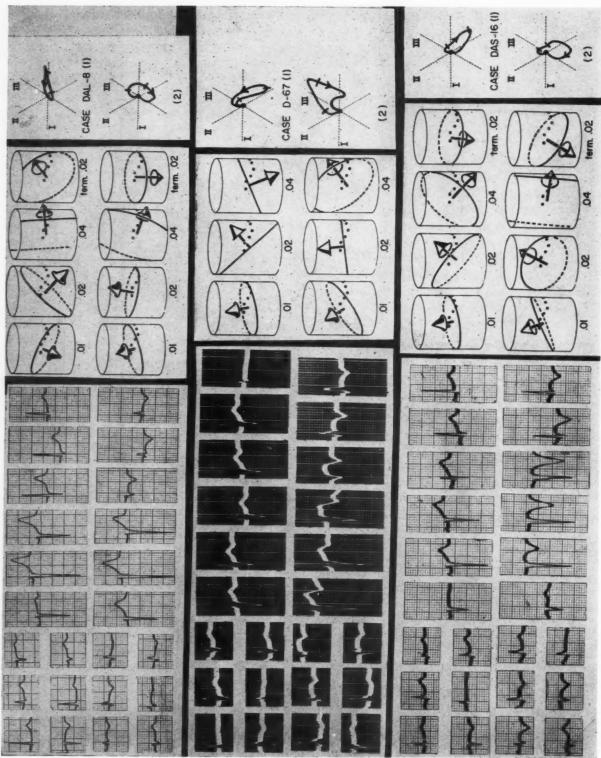


Fig. 8. Comparison of pre- and postinfarction tracings in three cases.

the cases described by First et al., there was little or no QRS complex prolongation in these cases. It must be presumed therefore that the region where excitation was delayed was normally excited during the first .04 second of the QRS interval and the delay was only .04 to .06 second in duration.

As a possible explanation for this type of periinfarction block one may consider the conduction network in the left ventricle as consisting of two pathways which are effectively syncytial with one another over large areas of the myocardium. Under normal circumstances excitation spreads simultaneously by both pathways during the first .04 second of the QRS interval.

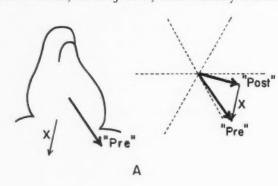
These two pathways correspond, perhaps, to the anterior and posterior subdivisions of the left bundle branch for which there is considerable anatomic and some physiologic evidence.^{7,8} Anterolateral infarcts tend to lie in the distribution of the anterior subdivisions and diaphragmatic infarcts tend to lie in the distribution of the posterior subdivisions. An infarct in one region would, if it involved a large enough portion of the network, cause excitation to spread largely by way of the other pathway so that excitation of the myocardium adjacent to the infarct would be delayed by .04 second but there would be little or no prolongation of the QRS interval. There are three observations which tend to support this concept: (1) The terminal vectors following anterolateral infarction do not point toward the infarcted region but to a region slightly posterior to it, as if the region of delayed depolarization did not overlie the infarct but lay just distal to it in a conduction sense. (2) The terminal vectors are usually relatively large in magnitude, indicating that the surface area of the delayed region must be quite large and perhaps larger than the surface area of the tissue overlying an average-sized infarct. (3) The terminal vector directions in the two types of peri-infarction block are remarkedly stereotyped from case to case, indeed considerably more stereotyped than the directions of the initial vector for each of the various locations of infarction.

There was another type of terminal vector abnormality encountered in this series which is believed to be due to a mechanism different from that of peri-infarction block. It is uncommon, having been seen in only three cases in the entire series, yet in each case there were several tracings at each stage of its evolution so that its

characteristics are well documented. Case AL-43 in Figure 6, a case of anterolateral infarction, is an example of this. In the first postinfarction tracing both initial and terminal vectors are altered in direction without QRS prolongation. But, unlike peri-infarction block, the terminal vectors have the same direction as the initial vectors. Thus all resultant electrical forces during the QRS interval are directed rightward and inferiorly. A possible explanation for this parallel deformity of initial and terminal vectors is that both endocardial and epicardial regions of the infarct have become electrically inert and therefore both the initial and the terminal vectors tend to point away from the location of the infarct. In other words, the infarct has become transmural in an electrical sense. In the case illustrated this type of deformity lasted one month at which time the infarct extended further laterally, as indicated by the change in direction of the initial vectors in the third tracing. With this extension the terminal vectors rotated to the direction which is characteristic of peri-infarction block in anterolateral infarction. In another case the transmural effect lasted only four days when, without evidence of extension, it was replaced by typical peri-infarction block of anterolateral infarction. It may be assumed that in this case the electrical effects of infarction were transmural only transiently.

3. Effect of the Directions of QRS Forces Prior to Infarction upon the Type of QRS Deformity Produced by Infarction. The directions which the initial QRS vectors are caused to take following infarction must depend to a certain extent upon their directions prior to infarction. For example, assume that of two subjects, A and B in Figure 9, in one the initial QRS vector prior to infarction is directed vertically, while in the other it is directed horizontally (pre and pre'). Then assume each acquires the same sized infarct in exactly the same region of the heart. The electrical forces which were generated from this region prior to infarction would be exactly the same in magnitude and direction and can be expressed by the "infarct vectors" (X and X'). The postinfarction initial vector equals the preinfarction vector minus the electrical activity removed by the infarct. Therefore, by using the parallelogram method of vector addition and subtraction in these two examples, one can subtract the infarct vector from the preinfarction vector to determine the direction of the post infarction vector for each case (post and

post'). In subject A it can be seen that the infarct has produced a postinfarction vector which is relatively horizontal; as shown in the triaxial diagram this will produce a Q wave on lead III but no Q wave in the other limb leads. On the other hand, in subject B, with exactly the same



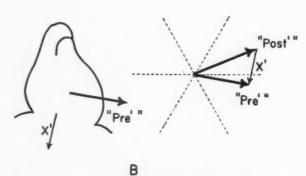


Fig. 9. Diagram illustrating the effect of the preinfarction QRS electrical force upon the type of QRS electrical force deformity which is produced by infarction. In case A (above) the preinfarction force is relatively vertical while in case B (below) the preinfarction force is more horizontal. See text for discussion.

location of infarction, the postinfarction vector is directed more superiorly, producing Q waves in lead π and aVF as well as lead π .

Given the pre- and postinfarction tracings in a given clinical case the reverse of this procedure must be followed. That is, the postinfarction vector is subtracted from the preinfarction vector to determine the direction and magnitude of the electrical activity removed by the infarct—the "infarct vector." Since this is the electrical activity removed by the infarct it will, according to present theory of cardiac excitation, point toward the region of the heart where the infarct has produced its electrical effect, and perhaps therefore it points toward the infarct itself. Such a calculation from the conventional tracing is necessarily extremely crude and it requires technically perfect tracings. However, one can roughly tell the site of the electrical defect simply

by noting the directional change of the vectors during the first .04 second of the QRS interval by comparing the pre- and postinfarction vector plots. For example, in Case DAS-16 in Figure 8 it can be seen that each of the instantaneous vectors has become rotated posteriorly from its preinfarction direction. Therefore the infarct had its principal electrical effect in the anterior portion of the left ventricle, according to current theory of the way in which infarction alters QRS electrical forces.⁸

In the majority of cases the location of the electrical defect was reasonably similar to the location one would have anticipated from the distribution of Q waves in the conventional tracing by assuming that the electrode locations where the abnormal Q waves were recorded overlie the location of the electrical defect. However, there were three circumstances in which the distribution of Q waves in the postinfarction tracing was misleading as to the electrical location of the infarct. One of these was seen in the cases called anterolateral infarction from the postinfarction tracing. This was described earlier in connection with Case AS-7 in Figure 5 where it was pointed out that although the conventional leads in the postinfarction tracing are those of anterolateral infarction, the change in vector direction is that of a strictly anterior infarction. There were seven other examples of this among the thirty-seven cases called anterolateral infarction from the postinfarction tracing.

The other two situations in which the postinfarction tracing was misleading as to the location of the electrical defect were in the diaphragmatic infarct group of cases. Among the ninety-nine cases called diaphragmatic infarction from the postinfarction tracing, there were thirty-one cases in which, in addition to significant Q waves in leads II and III, there were Q waves of .04 second's duration in certain of the precordial leads. Those with Q waves at V₁ and V₂ are generally considered to represent infarction of an anterior region of the diaphragmatic surface of the heart. Those with Q waves at more lateral precordial electrode positions in addition to leads 11 and 111 are usually considered to represent infarctions of more apical regions of the diaphragmatic surface of the heart.

However, when the direction of the initial vectors in the preinfarction tracings were studied in these thirty-one cases, it was found that over 50 per cent had .01 and .02 second vectors which

were superiorly directed prior to infarction. This direction was seen in less than 10 per cent of preinfarction tracings in the series as a whole. Case D-67 of Figure 8 is an example of this and illustrates that when the initial QRS vectors are superiorly directed before infarction a conventionally located diaphragmatic infarct will cause these initial vectors to point even more superiorly than is usually the case following diaphragmatic infarction. It is this more markedly superior direction of the vectors during the first .04 second of the QRS interval that produced the Q waves in the more lateral precordial leads in this case. There were eight other examples of this among the twenty-four cases called "apical" diaphragmatic infarction from the postinfarction tracing.

On the other hand, among seventeen cases called anterodiaphragmatic infarction from the postinfarction tracing there were nine cases in which the initial QRS vectors were superiorly directed prior to infarction. Comparison of the pre- and postinfarction directions of the initial QRS vectors in these cases showed that there had been little or no change in the frontal plane directions of these vectors and the principal change was the posterior rotation of the initial vectors. This is illustrated by Case DAS-16 of Figure 8. The principal change in the early vectors in this case is their posterior rotation, so the electrical defect is more strictly anterior in location than diaphragmatic.

Using this method for identifying the location of the electrical defect, all cases in this series were reviewed to see what the distribution of the electrical defect was for all types of infarction. The findings are indicated in Figure 10.

This distribution indicates that with current QRS criteria for myocardial infarction only those cases with electrical lesions on the anterior and diaphragmatic surfaces of the heart are recognized. (There were three cases of strictly posterior infarction from the postinfarction tracing which were not included in the analysis: they probably represented diaphragmatic infarction which included posterior portions of the left ventricle.) On the other hand, it is well to remember that only those cases which showed QRS complex or ST-T wave alterations currently accepted as "diagnostic" of infarction were studied. It is altogether possible that there are other types of QRS deformity which infarction can produce but are not recognized and therefore were not included in this series.

The distribution of the electrical defects in this series of cases somewhat parallels the outline of the septum. It is probable, then, that current QRS criteria for myocardial infarction will identify lesions which have an electrical effect on or relatively adjacent to the septum. This leaves a considerable portion of the left ventricle unac-

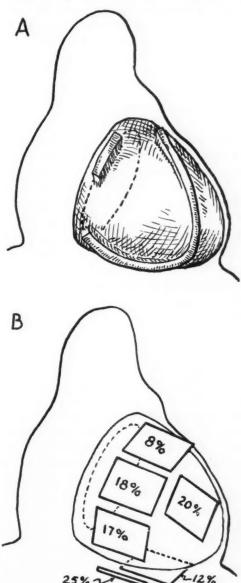


Fig. 10. A, schema showing the position of the left ventricle in the chest. The heart is viewed frontally, with the patient recumbent. The free wall of the right ventricle has been removed at its line of attachment to the left ventricle. It can be seen that the septum (the portion of the left ventricle to which the right ventricle attaches) faces anteriorly in its upper part and inferiorly in its lower part. The dotted line outlines the mitral-aortic orifice. B, the effective location of the electrical defect of infarction in 187 cases, calculated by the method described in the text.

counted for, as far as infarction is concerned. Perhaps this is one of the reasons why present QRS criteria for the recognition of myocardial infarction do not identify all the infarcts seen at

autonev

On the other hand, it is important to remember that the anatomic site of infarction is not necessarily identical with its electrical location. The two are, after all, different manifestations of the infarction process. The early stages of ventricular depolarization being a nearly instantaneous process, 9-11 it is possible to conceive of conduction relationships which would cause infarcts in various regions of the heart to be referred electrically to more proximate regions along the anterior and posterior subdivisions of the left bundle branch network. In any case it is important to note that all cases in the present series showed abnormality in direction of the very first QRS electrical force following infarction. Therefore, it must be concluded that, whatever the anatomic location of the infarct, its electrical mechanism must be such that the very first part of the myocardium to generate electrical activity of sufficient magnitude to be recorded at the body surface is involved by the infarction process.

CONCLUSIONS

1. Two approaches are used to study the QRS complex deformity produced by myocardial infarction. In the first approach vector methods are used to compare the distribution of electrical positivity and negativity on the chest surface for several instants during the QRS cycle in thirty-eight normal subjects with that in seventy-seven subjects with QRS complex deformity of myocardial infarction. In the second approach pre- and postinfarction tracings are compared by vector methods in 187 subjects as a controlled study of the QRS complex defect produced by infarction.

2. From the results of the first analysis a systematic method is described for cataloging infarcts from the distribution on the chest of the area of electrical negativity for the first .04 second of the QRS interval (the region of the chest where Q waves of .04 second would be recorded in unipolar leads). The empiric Q wave criteria currently used for the diagnosis of infarction are reformulated in electrical terms and a rational method for studying abnormal

or suspicious Q waves is described.

3. From the results of the second part of this

study it is concluded that in 95 per cent of cases of infarction in which QRS deformity is produced, at least the first .04 second of the QRS interval is deformed. This means that from a pattern point of view a Q wave should be at least .04 second in duration in a given lead before it can be considered diagnostic of myocardial infarction. Other types of deformity in addition to Q waves which infarction may produce in the first part of the QRS complex are described.

4. Four types of deformity of the terminal part of the QRS complex without prolongation of the QRS interval were encountered in association with myocardial infarction. Two of these are considered to be types of peri-infarction block. They were seen in nearly a third of the cases in the series, depending upon the electrical

location of the infarct.

5. The effect of the direction of the QRS electrical forces prior to infarction upon the distribution of Q waves which infarction of a given location in the heart will produce was studied. From this analysis it was possible roughly to determine the effective location of the electrical defect within the heart in each case. It was found that, whatever the actual anatomic location of the infarct, it must have an electrical effect upon the septum or paraseptal regions of the heart and must also involve the very first part of the heart to undergo depolarization in order to produce the QRS complex deformities of a type which is currently considered diagnostic of infarction. This represents only a part of the entire left ventricle and perhaps helps to explain why only a limited number of infarctions proved at postmortem examination are recognized electrocardiographically with present day criteria. The use of vector methods in future pathologic-electrocardiographic correlation studies should greatly improve these criteria.

REFERENCES

- 1. Grant, R. P. and Estes, E. H. Spatial Vector Electrocardiography. Philadelphia, 1951. Blakiston Co.
- Dodge, H. T. and Grant, R. P. Unpublished studies.
- Grant, R. P. Relationship between the anatomic position of the heart and the electrocardiogram. Circulation, 7: 890, 1953.
- LEVY, L., JACOBS, H. J., CHASTANT, H. P. and STRAUSS, H. B. Prominent R wave and shallow S wave in V-1 as a result of lateral wall myocardial infarction. Am. Heart J., 40: 447, 1950.

 ELEK, S. R., ALLENSTEIN, B. J., KORNBLUTH, A. W., GRIFFITH, G. C. and LEVINSON, D. C. Spatial vectorocardiogram in myocardial infarction typi-

AMERICAN JOURNAL OF MEDICINE

- fied by prominent R waves in leads aVr and V-1. Am. Heart J., 47: 477, 1954.
- FIRST, S. R., BAYLEY, R. H. and BEDFORD, D. R. Peri-infarction block; electrocardiographic abnormality occasionally resembling bundle branch block and local ventricular blocks of other types. Circulation, 2: 31, 1950.
- 7. WIDRAN, J. and Lev, M. The dissection of the atrioventricular node, bundle, and bundle branches in the human heart. *Circulation*, 4: 863, 1951.
- 8. Wilson, F. N., MacLeod, A. C. and Barker, P. S.
 Interpretation of the initial deflection of the
- ventricular complex of the electrocardiogram. Am. Heart J., 6: 637, 1931.
- 9. Trautwein, W. Experimentelle Untersuchung zur Theorie des Schenkelblock. EKG. Ztschr. ges. exper. Med., 117: 204, 1951.
- SHER, A. M., YOUNG, A. C., MALMGREN, A. L. and PATON, R. R. Spread of electrical activity through the wall of the ventricle. *Circulation Res.*, 1: 539, 1953.
- Burchell, H. B., Essex, H. E. and Pruitt, R. D. Studies on the spread of excitation through the ventricular myocardium. *Circulation*, 6: 161, 1952.

Studies on the Mechanism of Ventricular Activity*

VIII. The Genesis of the Coronary QS Wave in Through-and-through Infarction

Myron Prinzmetal, M.D., Rexford Kennamer, M.D. and Morton Maxwell, M.D.†

Los Angeles, California

ELECTROPHYSIOLOGIC theory concerning the genesis of coronary QS waves was originally formulated by Wilson and his associates. In a classic experimental study^{1a} these workers recorded epicardial and cavity leads from infarcted ventricles in the dog. The epicardial surface over through-and-through infarcts yielded pure negative deflections strikingly similar to the QS waves recorded from the ventricular cavity. It was therefore concluded that coronary QS complexes result from unaltered transmission of the negative cavity potential through a "hole" or "window" of dead muscle to the ventricular surface. ^{1b}

The coronary QS wave is universally regarded as the only unequivocal electrocardiographic sign of through-and-through muscle death.^{2,3} Wilson's observations on the genesis of this complex thus represent one of his most notable contributions to scientific electrocardiography. Direct confirmation of these observations, however, has not yet been reported.

By utilizing newer electrocardiographic technics it is now possible to devise a test of classic theory concerning the origin of coronary QS waves. The test consists of comparing surface and cavity leads with intramural tracings from various depths of an infarct. If negative cavity potentials are transmitted unaltered to the ventricular surface, identical potentials should occur at all levels from cavity to epicardium. Essentially similar QS waves thus would appear in cavity, intramural and epicardial leads. If the

complexes in these leads are dissimilar, unaltered transmission of the cavity potential must not occur. This reasoning is applied in the following analysis of tracings from through-and-through infarcts.

MATERIALS AND METHODS

The experimental methods used to produce and study myocardial infarction have been described in detail elsewhere. 4a In each of sixtyeight dogs the anterior descending coronary artery was ligated. Chronic infarcts were allowed to develop over a period of several days, weeks or months. Electrocardiographic examinations were then carried out. After routine precordial tracings had been made, multiple direct epicardial leads were recorded from the surface of the infarct. A cavity lead was registered simultaneously with each epicardial tracing. In most experiments intramural leads were recorded from various levels directly beneath the epicardial lead-point. A tiny plunge electrode which registers essentially local potentials was used to obtain the intramural and cavity records.

A test for injury currents was made by applying pressure to each epicardial lead-point. This technic, utilized by Wilson and associates, ¹⁰ demonstrates whether or not the local myocardium is completely dead. If viable muscle persists near the electrode, pressure causes elevation of the S-T segment. Isoelectricity returns promptly with cessation of pressure. If the muscle is completely dead, pressure does

^{*} From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Medicine, University of California School of Medicine, Los Angeles, Calif. Aided by grants of the United States Public Health Service and the L. D. Beaumont Trust Fund. Presented before the American College of Chest Physicians, California Chapter, Dec. 2, 1951; the Society for Experimental Biology and Medicine, Feb. 7, 1952, and the Boston City Hospital, May 9, 1952

[†] Research Fellow, American Heart Association.

not affect the S-T segment. Similarly, insertion of the sharp-tipped plunge electrode causes S-T segment elevation in intramural leads from viable muscle. The segment gradually returns toward the baseline, becoming isoelectric or reaching minimal amplitude within two to ten minutes. If the intramural muscle is completely dead, S-T segment deviation does not occur in the intramural tracing. The injury current test thus can be used to show the status of intramural as well as epicardial muscle.

High speed cinematographs of sixteen ventricles were recorded after the electrocardiographic exploration. The cinematographs provide direct evidence concerning the effect of infarction on ventricular contractility. Marked ballooning of the ventricular surface characterizes the appearance of non-contractile regions while other portions of the ventricle are in systole.

Upon completion of the electrocardiographic and cinematographic studies the infarcted ventricles were removed and sectioned. Histologic slides of selected regions were then made. All slides were examined "blind"; that is, the observer did not know the electrocardiographic data obtained from the muscle under the microscope. After each slide had been graded the electrocardiographic and pathologic data were compared. An excellent correlation was noted between the results of injury current tests and the histologic status of the myocardium. The muscle which failed to yield injury currents always appeared completely fibrotic or necrotic. Conversely, the sites yielding elevated S-T segments consistently showed histologic evidence of viability.

RESULTS

Of the sixty-eight infarcts in the series more than half did not reveal histologically demonstrable through-and-through muscle death. Most of the remaining infarcts were excluded from the present analysis for one of the following reasons:

(1) The region of through-and-through infarction appeared extremely narrow. (2) Well stained histologic slides of the region were not available. (3) Complete electrocardiographic data had not been obtained from the through-and-through portion of the lesion. When these instances had been eliminated, sixteen through-and-through infarcts remained.

Pathologic Data. The sixteen infarcts were studied from 11 to 136 days after coronary

artery ligation. In each instance histologic examination disclosed a broad area completely devoid of viable muscle. These areas consisted entirely of fibrotic and/or necrotic tissue extending from endocardium to epicardium. The relative amounts of fibrosis and necrosis varied with the age of the infarct. Fibrosis predominated in the older lesions while the lesions of shorter duration were primarily necrotic. Most of the regions of through-and-through infarction were bordered on either side by patches of live muscle or by subendocardial extensions of the infarct. As shown by comparison with normal muscle in the same slide, the regions of through-and-through death had undergone some shrinkage in the thickness of the wall. A rough correlation between the degree of shrinkage and the age of the infarct was usually but not invariably observed.

Electrocardiographic Data. Tracings were recorded from the epicardium directly over and from the cavity directly under each region of through-and-through infarction. Intramural leads from several levels of each region also were obtained. As shown in Figures 1 and 2 the epicardial, intramural and cavity tracings consistently presented pure QS waves. In each instance the intramural and cavity complexes appeared identical in magnitude and configuration. The epicardial complex was identical with the intramural and cavity complexes except for the occasional occurrence of a somewhat deeper epicardial deflection. All levels of the throughand-through infarct thus yielded QS waves identical or almost identical with the cavity QS.

For purposes of timing, all tracings from a given infarct were recorded simultaneously with the same cavity lead. The records were made at the rapid paper speed of 125 mm. per second, thus making possible accurate comparisons of timing. In every instance the QS waves began simultaneously in epicardial, intramural and cavity leads.

Isoelectric S-T segments and upright T waves were recorded from all levels of the sixteen through-and-through infarcts. (Figs. 1 and 2.) Pressure on the surface of the lesions always failed to cause S-T segment elevation in the epicardial leads. Manipulation of the plunge electrode at intramural levels likewise failed to elicit injury currents. Heating of the epicardium did not alter the T wave. In contrast, these procedures consistently yield S-T segment and T wave changes in leads from normal or partially damaged muscle. 4.5 Hence the absence of viable

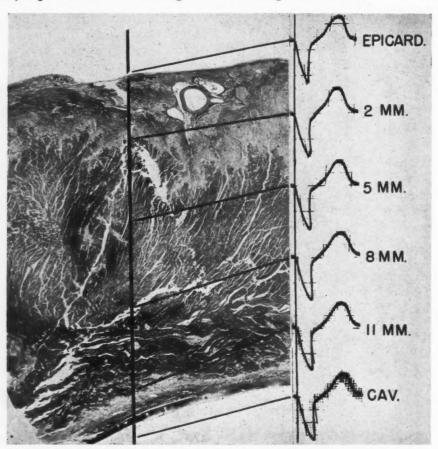


Fig. 1. Histologic section and electrocardiograms from infarct produced by coronary artery ligation. Tracings recorded at paper speed of 125 mm. per second. Sensitivity: 20 mv. equal 15 mm. Black line represents path of plunge electrode. Fibrotic or necrotic tissue appears whitish-gray, live cardiac muscle grayish-black. Section shows through-and-through infarct. No live muscle remains in region of plunge electrode. Epicardial QS wave is essentially identical in timing, magnitude and configuration with intramural and cavity QS waves. Isoelectric S-T segments and upright T waves also appear identical in all leads.

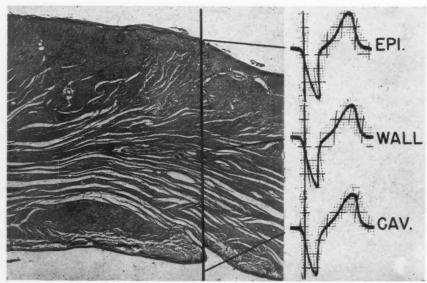


Fig. 2. Epicardial, intramural and cavity leads from region of through-and-through infarction produced by coronary artery ligation. Muscle is completely infarcted at all levels from endocardium to epicardium. Identical QS waves, isoelectric S-T segments and upright T waves are seen in all leads.

tissue in the sixteen regions of through-andthrough infarction was demonstrated by electrocardiographic as well as histologic methods.

Cinematographic Data. High speed cinematographs consistently failed to show contractions in regions of through-and-through muscle death. As compared with adjacent areas, the surface of the through-and-through infarct appeared to balloon during systole. This direct evidence of impaired contractility confirmed the absence of viable muscle in the underlying wall.

The preceding data are entirely consistent with Wilson's observations on through-and-through infarction. All sixteen through-and-through lesions yielded epicardial and intramural QS waves essentially identical with the cavity complex. In these instances, therefore, the coronary QS waves must have resulted from unaltered transmission of cavity negativity through completely dead muscle to the surface of the heart. A second type of coronary QS wave which does not result from unaltered transmission of cavity potentials will be discussed in the

following paper. The use of "plunge" electrodes to record intramural leads from inside the ventricle is relatively new. Epicardial and cavity leads, on the other hand, have been employed for many years and are generally regarded as a reliable method of registering local potentials. The reliability of the intramural lead technic thus may be tested by comparing intramural tracings with epicardial and cavity tracings. Since the sixteen through-and-through infarcts observed in the present study were devoid of live muscle, all levels of the ventricle from endocardium to epicardium must have presented the same potential as the cavity. Therefore, if the plunge electrode accurately recorded potentials within the infarct, the intramural tracings would be identical with the epicardial and cavity tracings. Conversely, if significant artifacts were present in the intramural tracings, they would have differed markedly from the epicardial and cavity tracings. Actually, the intramural, epicardial and cavity complexes were always identical or almost identical. Hence the plunge electrode was shown to register accurately local intramural potentials in infarcted muscle. As reported previously4b a comparable observation was made in uninfarcted hearts by recording intramural leads immediately above the endocardium simultaneously with cavity leads from directly subjacent sites. Essentially similar complexes occurred in the intramural and cavity tracings. Intramural leads recorded immediately below the epicardium likewise showed complexes almost identical with those in epicardial leads from directly superjacent sites. Since the cavity and epicardial records presumably were accurate, any significant artifacts in the subendocardial or subepicardial tracings would have caused them to differ, respectively, from the cavity or epicardial tracings. Thus the technic of intramural lead electrocardiography appears to provide a reliable means of recording local potentials in normal as well as in infarcted ventricles.

SUMMARY

The electrocardiogram of through-andthrough infarction was studied in sixteen dogs with chronic lesions produced by coronary artery ligation. Failure to elicit injury currents at epicardial and intramural levels established the absence of viable muscle within the infarcted regions. Histologic examination confirmed that the regions were completely dead.

Direct leads from the epicardium and from various intramural levels of each region yielded pure QS waves identical or almost identical with the cavity QS complex. This observation indicated that the negative cavity potential was transmitted unaltered through the infarct, causing the coronary QS wave.

REFERENCES

- (a) Wilson, F. N., Johnston, F. D. and Hill, I. G. W. Interpretation of the galvanometric curves obtained when one electrode is distant from the heart and the other near or in contact with the ventricular surface. II. Observations on the mammalian heart. Am. Heart J., 10: 176, 1934. (b) Wilson, F. N., Rosenbaum, F. R. and Johnston, F. D. Interpretation of the Ventricular Complex of the Electrocardiogram. Advances in Internal Medicine, vol. II, New York, 1947. Interscience Publishers, Inc.
- Lepeschkin, E. Modern Electrocardiography, vol. I. Baltimore, 1951. Williams and Wilkins Co.
- BARKER, J. M. The Unipolar Electrocardiogram: A Clinical Interpretation. New York, 1952. Appleton-Century-Crofts, Inc.
- 4. (a) Prinzmetal, M., Kennamer, R., Shaw, C. McK., Kimura, N., Lindgren, I. and Goldman, A. Intramural depolarization potentials in myocardial infarction: a preliminary report. Circulation, 7: 1, 1953. (b) Kennamer, R., Bernstein, J. L., Maxwell, M. H., Prinzmetal, M. and Shaw, C. McK. Studies on the mechanism of ventricular activity. v. Intramural depolarization potentials in the normal heart with a consideration of currents of injury in coronary artery disease. Am. Heart J., 46: 3, 1953.
- SHAW, C. McK., GOLDMAN, A., KENNAMER, R., KIMURA, N., LINDGREN, I., MAXWELL, M. H. and PRINZMETAL, M. Studies on the mechanism of ventricular activity. vii. The origin of the coronary QR wave. Am. J. Med., 16: 490, 1954.

Studies on the Mechanism of Ventricular Activity*

IX. The "Mural-type" Coronary QS Wave

MORTON MAXWELL, M.D., † REXFORD KENNAMER, M.D. and MYRON PRINZMETAL, M.D.

Los Angeles, California

Thas been noted in the preceding paper¹ that regions of through-and-through infarction yield epicardial QS complexes identical in timing and configuration with the QS waves in intramural and cavity leads from subjacent sites. This observation confirms the general belief, originally proposed by Wilson,² that the negative cavity potential is transmitted unaltered through the "hole" of dead myocardium to the epicardial surface, resulting in a "cavity-type" coronary QS wave.

Of the coronary QS waves recorded in the present study of sixty-eight chronic infarcts less than half were of the cavity type. A second type of coronary QS wave was frequently found which, unlike cavity-type QS waves, did not occur over through-and-through infarcts. Instead, these deflections appeared over regions presenting histologic, electrocardiographic and physiologic evidence of viability. Since such QS waves cannot represent unaltered transmission of cavity negativity, they must be at least partially determined by electrical activity of live muscle in the ventricular wall. They may therefore be termed "mural-type" coronary QS waves

The mural-type QS complexes discussed in this paper may represent a clinically important electrocardiographic aberration worthy of detailed analysis. According to classic theory, pure QS waves occur when the entire thickness of the ventricle beneath the electrode is completely dead. The present study shows that these deflections also often appear when significant amounts of viable muscle remain within the

underlying wall. In many patients, therefore, coronary QS waves may indicate less grave myocardial damage than previously supposed. The following correlation of histologic, electrocardiographic and cinematographic data from ventricular regions yielding mural-type QS waves thus should be of practical as well as theoretic interest. Also included in the report are (1) a series of relatively acute experiments in which electrocardiograms were made within forty-eight hours after ligation of the coronary artery and (2) studies designed to demonstrate the electrocardiographic changes associated with destruction of the outer ventricular layers.

PART I. THE MURAL-TYPE QS WAVE IN CORONARY
ARTERY DISEASE

As described elsewhere, 3-5 chronic myocardial infarcts were produced in sixty-eight dogs by ligation of the anterior descending coronary artery and studied by electrocardiographic, cinematographic and histologic technics. Those experiments which fulfilled the following criteria were selected for the present analysis of muraltype QS waves: (1) Pure QS waves appeared in at least one epicardial lead despite the presence of live muscle in the underlying wall. Complexes with embryonic r waves or marked notches on the downstroke or upstroke were excluded. (2) A cavity lead and intramural leads from several depths were recorded directly beneath the epicardial lead-point. (3) Well stained histologic sections of the transmural region beneath the epicardial lead-point were available for correlative study. Classification of the histologic

^{*} From the Institute for Medical Research, Cedars of Lebanon Hospital, and the Department of Medicine, University of California School of Medicine, Los Angeles, Calif. Aided by grants of the United States Public Health Service and the L. D. Beaumont Trust Fund. Presented before the American College of Chest Physicians, California Chapter, Dec. 2, 1951; the Society for Experimental Biology and Medicine, Feb. 7, 1952; the Boston City Hospital, May 9, 1952.

[†] Research Fellow, American Heart Association.

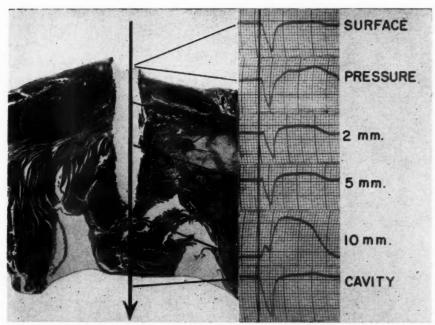


Fig. 1. Histologic section and electrocardiograms from infarct produced by coronary artery ligation. Tracings recorded at paper speed of 125 mm. per second. Arrow represents path of plunge electrode used to register intramural leads. Infarcted tissue appears grayish white, live cardiac muscle grayish black. Transmural infarct is present to right. Large fibrous strand extends through region over which QS wave was recorded. Subendocardial layers of this region appear essentially normal. Epicardial lead (surface) exhibits mural-type QS wave followed by isoelectric S-T segment. Application of pressure near epicardial lead-point elicited injury currents, manifested by elevation of S-T segment (second tracing from top). Intramural leads recorded 2 mm. and 5 mm. below epicardium show tiny initial r waves followed by deep S waves. Marked S-T segment elevation in intramural lead from 10 mm. depth was registered immediately after insertion of plunge electrode. Cavity presents pure QS wave considerably deeper than epicardial QS wave. Both histologic appearance and elevated S-T segments at epicardial and subendocardial levels establish that live muscle remained within region yielding mural-type QS wave.

sections according to distribution and degree of pathologic disorder was done independently by three workers who were not acquainted with the electrocardiographic data obtained from the muscle under observation.

RESULTS

Because of the arbitrarily rigid criteria for selection, a total of only seventeen epicardial leads presenting mural-type QS waves was included in the analysis. These leads were recorded in fifteen hearts with infarcts ranging in age from eleven to forty-nine days after ligation of the coronary artery.

Pathologic Changes. Grossly, all of the fifteen hearts presented infarcts involving transmural portions of the left ventricle. The infarcts varied in size and location, the majority occurring in the anteroseptal wall.

Histologic examination of the transmural regions over which mural-type QS waves were registered showed some live muscle in every instance. Fourteen of the seventeen regions consisted of necrotic or fibrotic tissue, depending on the age of the infarct, mixed with live muscle

in variable locations and proportions. (Figs. 1 and 2.) Several of these regions exhibited approximately equal amounts of live and dead muscle throughout. In other instances patchy islets or strands of uninfarcted tissue appeared at various levels from endocardium to epicardium. Two regions containing both live and dead muscle were located precisely at the border between a transmural infarct and a subendocardial extension. The remaining three regions consisted entirely of viable muscle located immediately adjacent to the edges of transmural infarcts. In these instances the myocardium beneath the electrode was free from fibrosis and necrosis but was histologically altered.

The pathologic changes found in regions yielding mural-type QS waves differ from those associated with cavity-type QS waves. As described in the preceding paper, transmural sections of the myocardium beneath cavity-type QS lead-points were always entirely devoid of live muscle. In contrast, the regions which presented mural-type QS waves contained significant amounts of live muscle, usually interspersed with dead tissue. This contrast

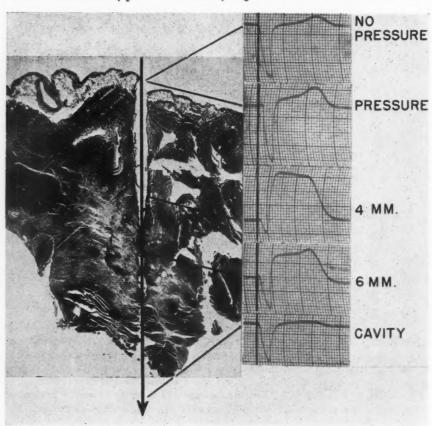


Fig. 2. Histologic section and electrocardiograms from left ventricle seventeen days after coronary artery ligation. Section consists of necrotic and fibrotic tissue interspersed with live muscle. Intramural leads were recorded immediately after insertion of plunge electrode. Elevated S-T segments appeared in epicardial tracing during application of pressure near lead-point and in intramural tracings from 4 mm. and 6 mm. depths. Presence of live muscle within region thus was demonstrated electrocardiographically as well as histologically. Epicardial QS wave exhibits more abrupt and deeper downstroke than cavity QS wave. (Paper speed 125 mm. per second.)

is clearly illustrated in Figure 3, showing a section over which both cavity-type and muraltype QS waves were recorded from adjacent sites. The region beneath the cavity-type QS lead-point is completely fibrotic, while the region beneath the mural-type QS lead-point exhibits variable amounts of live muscle. As compared with coronary QR waves the histologic changes associated with mural-type QS waves were similar in general pattern but were probably more pronounced; that is, the QS regions appeared to contain a somewhat greater proportion of dead tissue. The data concerning this problem were not, however, adequate for quantitative comparison. Histologic examination thus revealed that, contrary to classic theory, coronary QS waves may occur over regions containing variable amounts of live muscle as well as over regions which are completely dead.

Currents of Injury. In all seventeen epicardial leads exhibiting mural-type QS waves prompt elevation of the S-T segment occurred when pressure was applied near the lead-point. (Figs.

1 to 4.) This manifestation of injury current established the presence of live muscle in the vicinity of the epicardial electrode. 6 Elevated S-T segments also appeared in at least one intramural lead from each of the seventeen regions when the sharp-tipped plunge electrode was inserted, indicating that some intramural muscle was alive. (Fig. 4.) As in previous studies^{1,5} the information provided by injury currents correlated well with the histologic findings. Leadpoints which yielded elevated S-T segments showed uninfarcted tissue when later examined histologically. Conversely, muscle which failed to show injury currents during the experiments appeared completely fibrotic or necrotic under the microscope. The presence of viable muscle within regions yielding mural-type coronary QS waves thus was demonstrated electrically by injury currents as well as histologically.

Current of injury in association with coronary QS waves was further observed during a series of ten relatively acute experiments. The technics and procedures were identical with those

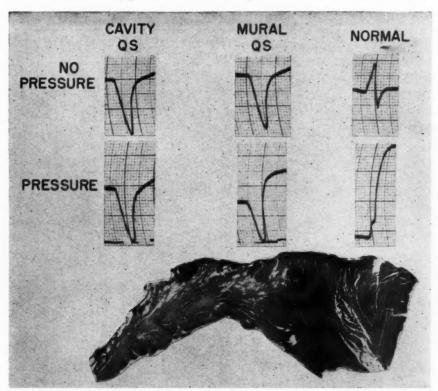


Fig. 3. Histologic section and electrocardiograms showing contrast between cavity-type and mural-type QS waves. Left-hand portion of section is completely fibrotic from endocardium to epicardium; central portion presents mixture of live and dead muscle; right-hand portion is completely normal. Epicardial lead recorded over completely fibrotic region exhibits cavity-type QS wave followed by isoelectric S-T segment which does not rise when pressure is applied near lead-point. Adjacent region also yields pure coronary QS wave but gives rise to injury currents, manifested by S-T segment elevation, upon application of pressure. Since this QS wave occurs over region containing remnants of live muscle capable of generating injury currents, it is of the mural type. Normal region at right presents epicardial Rs wave. As in region yielding mural-type QS wave, normal region gives rise to injury currents when pressure is applied to epicardium.

used in the study of chronic infarcts, except that the animals were examined within forty-eight hours after ligation of the coronary artery. At this early stage of infarction the histologic and electrocardiographic patterns are still in a transitional state. The infarcts were poorly defined, consisting of soft, hemorrhagic and necrotic myocardium. That viable muscle remained within the lesions was demonstrated by the persistence of spontaneous S-T segment elevation throughout the experiment. Despite this manifestation of injury current, QS complexes of varying configurations usually were recorded in epicardial leads over the infarcted regions. (Fig. 5.) These complexes were of the mural type inasmuch as the underlying myocardium was not completely dead.

As noted in the preceding paper, on no occasion could injury currents be elicited from regions of through-and-through infarction yielding cavity-type coronary QS waves. In regions yielding mural-type coronary QS waves, on the other hand, injury currents always appeared spon-

taneously if the lesion was acute and could be produced by trauma if the lesion was chronic. It was thus established that electrically active muscle remained within the underlying wall despite the occurrence of mural-type coronary QS waves.

Comparison of Epicardial and Cavity QS Complexes. A lead from within the left ventricular cavity beneath the infarct was recorded throughout each experiment simultaneously with each epicardial or intramural lead for purposes of timing. Tracings from more localized parts of the cavity directly beneath the regions yielding mural-type QS waves also were recorded in twelve instances. As compared with the QS wave in the subjacent cavity lead, the epicardial QS wave presented a wide variety of differences. (Fig. 6.) The epicardial complex sometimes started later and exhibited a more gradual downstroke than the cavity deflection. In other experiments, however, the epicardial and cavity QS waves began simultaneously. A few epicardial QS waves presented more abrupt and deeper

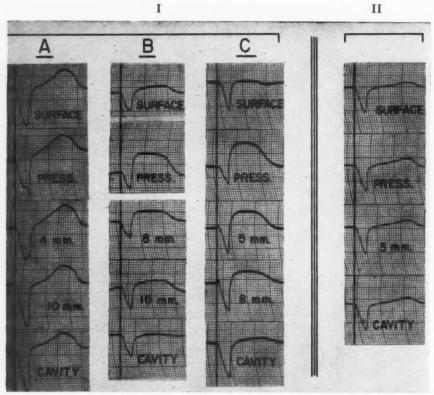


Fig. 4. (I) Epicardial surface, intramural and cavity leads from three regions presenting mural-type coronary QS waves. Marked S-T segment elevation occurred in epicardial tracings when pressure was applied near lead-points (second row of tracings). Intramural leads from various levels likewise exhibited S-T segment elevation immediately after insertion of plunge electrodes. These S-T segment changes established that live muscle remained within the regions yielding mural-type QS waves. Note that the epicardial, intramural and cavity complexes recorded from each region differ in timing and/or configuration. If negative cavity potentials were transmitted unaltered to the epicardium, identical QS waves should occur in cavity, intramural and epicardial leads. Electrical activity of live muscle within the underlying wall must therefore have affected the mural-type QS waves. (II) Epicardial, intramural and cavity leads from region of through-and-through infarction yielding cavity-type QS wave. Application of pressure near epicardial lead-point did not cause S-T segment elevation. Epicardial, intramural and cavity complexes are identical, establishing that negative cavity potential was transmitted unaltered through completely dead muscle to ventricular surface. These findings contrast strikingly with those illustrated in (I) A, B and C.

downstrokes than the cavity deflections. Only in a few instances did the epicardial and cavity complexes appear identical. These findings contrast with those noted in regions of through-and-through infarction¹ where identical complexes invariably occur in epicardial and subjacent cavity leads. The mural-type epicardial QS waves which differed from the underlying cavity complex must have been modified by viable intramural muscle between the epicardial and cavity lead-points.

Comparison of Epicardial and Intramural Complexes. Tracings from all levels of regions yielding cavity-type QS waves were identical. The intramural complexes from regions yielding mural-type QS waves, however, presented a variety of patterns. (Figs. 1, 2 and 4.) In general, intramural leads from different levels showed

QS waves of differing configurations and amplitudes. Although these often resembled either the epicardial or cavity complex, they sometimes differed from both and from each other in timing and/or shape. The subepicardial QS waves usually were more like those from the epicardium whereas the QS waves recorded from deeper intramural levels more often resembled the cavity deflection. In several experiments a marked slur appeared on the downstroke or upstroke of one or more intramural complexes. In other instances tiny r waves were recorded in some intramural leads despite the presence of purely negative deflections in tracings from overlying and underlying sites. The S-T segments and T waves, like the mural-type QS waves, often differed in leads from different levels of a given region. In contrast, regions of through-and-through infarction yielded identical S-T segments and T waves in epicardial, intramural and cavity leads.

Thus the seventeen instances which yielded mural-type QS waves showed no consistent pattern in the timing, configuration or amplitude of the intramural tracings recorded from different regions or even from different levels of the same region. Although the variations in the intramural QS waves were usually slight, they nevertheless contrast strikingly with the identical QS waves in intramural leads from regions of through-and-through infarction.

Cinematographic Observations of Contractility. As noted in the preceding paper, high speed cinematographs of the infarcted ventricle were recorded in sixteen experiments. The films always showed ballooning of areas yielding cavity-type coronary QS waves while other parts of the ventricle were in systole. This direct evidence established that the muscle beneath the QS lead-points was non-contractile. Portions of the ventricular surface from which mural-type QS waves were recorded also exhibited ballooning, indicating non-contractility, on most occasions. Several such cases, however, showed contractions. The contractile areas usually contained visible amounts of live muscle, appearing in the color cinematographs as patches of red interspersed with grey or white tissue. Areas composed entirely of scar tissue, in contrast, appeared greyish-white throughout and always ballooned during systole.

Three technics were used to differentiate contractile and non-contractile QS areas: (1) In profile views of the ventricle the silhouette of contractile areas wrinkled and drew inward during systole while adjacent non-contractile areas ballooned outward. These profile views revealed distinct contraction of four areas yielding mural-type QS waves. (2) In front views of the ventricle the surface veins and arteries curled during systole in the contractile QS areas and straightened in ballooning areas. (3) During several experiments the QS areas were circled with Janus green before cinematographs were taken in order to demonstrate changes in their size and shape. If the underlying muscle was contractile, the circle became smaller during systole. If the underlying muscle was non-contractile, the circle became larger as other parts of the ventricle contracted. Most of the circled QS areas grew larger during systole, indicating that the underlying myocardium was

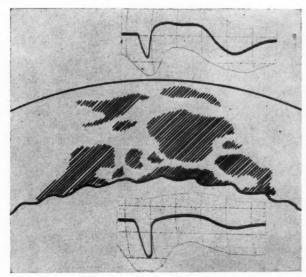


Fig. 5. Epicardial and cavity leads from left ventricle two days after coronary artery ligation. Infarct consists of patches of necrosis interspersed with live muscle. Pure QS waves appear in both leads but epicardial complex is shallower than cavity complex. S-T segment elevation in epicardial lead provides electrocardiographic evidence that live muscle remains under electrode despite occurrence of coronary QS wave.

not strong enough to contract. In a few cases, on the other hand, the QS area became smaller during systole, thus showing definite contractions. The remaining QS areas were constant in size throughout the cardiac cycle, suggesting that contractility of the underlying wall was impaired but was sufficient to prevent ballooning.

These cinematographic observations may help to explain certain discrepancies between the electrocardiographic and physiologic changes seen in patients after coronary artery occlusion. Most infarcted regions which yielded coronary QS waves were incapable of significant contraction, as evidenced by ballooning during ventricular systole. Several regions yielding similar complexes nevertheless exhibited distinct systolic contractions, indicating that they contained enough live muscle to function effectively although presumably with subnormal efficiency. This contrast was clearly shown in cinematographs of one infarct which presented cavitytype QS waves over the center and mural-type QS waves over the periphery. Although the complexes appeared similar, the center of the infarct ballooned while the periphery contracted. Thus the occurrence of coronary QS waves does not in itself reveal whether the underlying muscle has lost its function completely, partially, or perhaps only slightly.

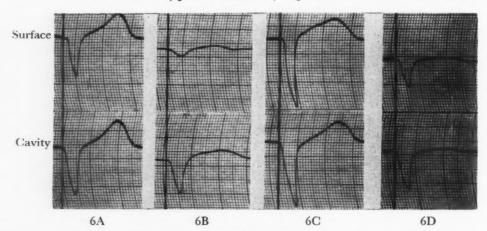


Fig. 6. Epicardial surface and cavity leads from four left ventricles eleven to twenty-eight days after coronary artery ligation. Each epicardial lead was recorded simultaneously with lead from subjacent cavity. Regions over which epicardial complexes were obtained presented variable mixtures of live and dead muscle. Pure QS waves in epicardial leads differ in timing and/or configuration from cavity QS waves. A, downstroke of epicardial complex starts later than cavity complex. B, epicardial QS wave is considerably shallower than cavity QS wave. C, as compared with cavity complex, epicardial QS wave starts later, presents more abrupt downstroke and is slightly deeper and narrower. S-T segment in epicardial lead is slightly elevated, demonstrating presence of live muscle near electrode. D, epicardial QS wave is shallower and starts later than cavity QS wave. Note slight slur on downstroke in epicardial lead which does not appear in cavity lead. Such differences between epicardial and cavity complexes were never observed in regions of throughand-through infarction which invariably yield identical QS waves at all levels from ventricular cavity to surface (see Fig. 4 II).

PART II. THE ELECTROCARDIOGRAPHIC EFFECTS OF DESTRUCTION OF THE OUTER VENTRICULAR LAYERS

Previous work reported from this laboratory⁴ has shown that chronic infarcts in dogs limited to the subendocardial region did not alter the normal R and RS waves in precordial or direct epicardial leads. The precordial tracings registered before the chest was opened often appeared entirely normal. Acute subendocardial lesions likewise failed to yield abnormal depolarization complexes. Contrary to classic theory, therefore, depolarization of the inner ventricular layers appeared to be "electrocardiographically silent." An explanation for this phenomenon was suggested by studies of the normal ventricle^{3,4,7}. 10,11 which revealed that the inner layers are depolarized instantaneously, or too rapidly to be measured with a variety of recording equipment. Local intramural leads from these layers presented pure QS waves resulting, like the cavity QS waves, from depolarization of other parts of the heart. Extension of Purkinje fibers into the myocardium was regarded as a possibility which might account for the rapid rate of depolarization at deeper levels of the wall.

It was inferred from these observations that the R wave recorded over the left ventricle results from depolarization of the outer layers and is independent of the status of the deeper myocardium. Hence an abnormal Q wave should occur when, and only when, the outer layers are damaged. This hypothesis was supported by an analysis of infarcted regions from which epicardial QR waves were recorded. No correlation was found between the status of subendocardial muscle and the abnormal Q waves. Rather, the common denominator, histologically, was the presence of some dead muscle in the outer ventricular layers beneath or near the epicardial electrode.

If the inner ventricular layers are electrocardiographically silent, destruction of the outer layers should produce abnormal Q waves even though the deeper muscle remains entirely intact. Because of the anatomic arrangement of the blood supply to the heart, occlusion of a major coronary artery usually results in greater damage to the endocardial than the epicardial region. Thus although seven pure subendocardial lesions occurred in the series of sixty-eight infarcts produced by coronary artery ligation, no instance was found in which the inner ventricular layers were completely undamaged. It was therefore necessary to employ other methods in order to determine if muscle death limited to the outer layers is sufficient to cause abnormal Q waves.

Three methods were used in an attempt selectively to destroy superficial portions of the ventricle without damaging the underlying

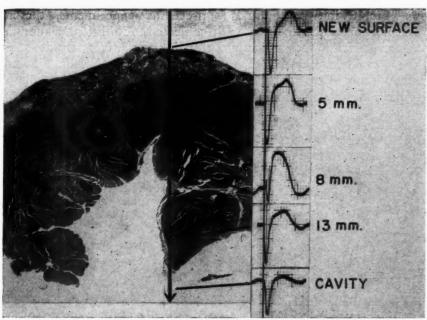


Fig. 7. Histologicel-ectrocardiographic appearance of region of left ventricle from which outer few millimeters were removed by surgical excision. New surface of region consists of scar tissue. Inner layers are completely normal. Lead from new surface exhibits pure QS wave despite intact subendocardium (paper speed 75 mm. per second).

subendocardium: (1) injection of formaldehyde, (2) application or injection of nitric acid and (3) epicardial excision. In 1934 experiments of similar design were performed by Bellet and Johnston⁸ who cauterized the left ventricular surface in dogs. These authors noted replacement of the normal RS complexes by QS waves in epicardial and precordial leads following cauterization.

Formaldehyde. In six animals 2 to 5 cc. of 20 per cent formaldehyde was injected into the pericardial sac. The chests were then closed and precordial leads from several interspaces as well as limb leads were taken daily. Three of these animals showed QS and/or QR waves in several precordial leads on the second day. The Q waves disappeared within twenty-four to forty-eight hours. The other three animals presented no significant electrocardiographic changes. At the end of two weeks the animals were sacrificed and several sections taken from the left ventricle for histologic study. A thin layer of damaged muscle at the epicardial surface generally was present but could not be easily distinguished histologically, appearing merely as a somewhat more intense shade of pink in the hematoxylin and eosin stain without disruption of muscle fiber arrangement.

Nitric Acid. Since the damage produced by injection of formaldehyde appeared inadequate, a new series of experiments was undertaken. The

hearts of twenty dogs were widely exposed during anesthesia and respiration maintained with an artificial pump respirator. After electrocardiographic exploration, concentrated or halfstrength nitric acid was applied repeatedly to localized areas of the left ventricular surface, care being taken to avoid the major coronary arteries and their branches. The traumatized regions became vellowish-brown immediately, providing delineation of the areas to be studied. Multiple direct leads from the affected epicardium and nearby sites were then recorded at frequent intervals for as long as three hours. At the termination of the experiment sections were taken for microscopic examination. Injury currents, persisting throughout many experiments, made the tracings difficult to interpret. In most instances the main electrocardiographic change seemed to be a diminution in the amplitude of the R wave, without the appearance of abnormal Q waves. Histologic sections revealed that only a very thin epicardial layer was destroyed despite several applications of nitric acid.

In two experiments 1 cc. of nitric acid was injected as a bleb beneath the epicardium. One of these animals showed QS waves over and QR waves at the edges of the damaged area. Sections from the region demonstrated that the inner two-thirds of the ventricular wall was histologically normal.

Epicardial Excision. Finally, in twelve animals superficial layers of a portion of the anterior or lateral wall of the left ventricle were surgically excised and the chest closed aseptically. The dogs were re-examined between ten and fifteen days following the excision. After routine limb

preceding experiments, therefore, cannot be subjected to statistical or mathematical analysis, but rather must be considered individually. The appearance of epicardial QS and QR waves over viable subendocardial muscle in any single instance thus appears significant.

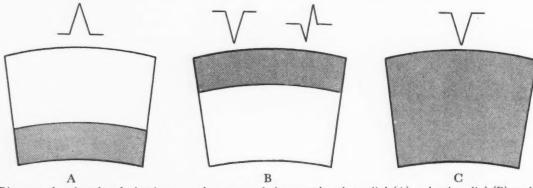


Fig. 8. Diagram showing depolarization complexes recorded over subendocardial (A), subepicardial (B) and through and-through (C) lesions. Dead muscle is shaded. A, inner layers are dead; outer layers are viable. Normal R wave occurs over ventricle. B, outer layers are damaged; inner layers are normal. Either mural-type QS waves or QR waves may appear over ventricle, presumably depending on proportion of live and dead muscle under electrode. C, all layers from endocardium to epicardium are completely dead. Cavity-type coronary QS wave is recorded.

and precordial leads had been made the hearts were exposed and the entire ventricular surface explored electrocardiographically, with many leads recorded over and around the ablated regions. Sections were then taken for histologic correlation. In six instances necrosis and fibrosis extended deeply into the subendocardial layers or actually reached the endocardial surface; these experiments were excluded from consideration. In sections from the remaining six experiments, however, the inner ventricular layers appeared histologically normal or only mildly altered. Direct leads recorded over the ablated regions in four of these six instances presented marked alterations of the epicardial complexes consisting of QS, slurred QS, QR or abnormal rS waves. (Fig. 7.) Leads over the damaged areas in the remaining two animals presented R or Rs complexes probably within normal limits.

It should be recognized that the many difficulties inherent in surgical destruction of the outer ventricular layers (hemorrhage, avoidance of major coronary vessels, variations in heart size) made it impossible to cut out precisely comparable proportions of the wall in these animals. In general, the excised tissue measured approximately 1.5 by 1.5 cm. in area and was 2 to 5 mm. thick in its central portion, regardless of the size of the heart. Necrosis of varying amounts usually developed in the myocardium underlying the site of excision, probably owing to interference with local coronary circulation. The

Figure 8 contrasts the electrocardiographic effects of destruction of the inner and outer ventricular layers. This simple diagram summarizes the observations discussed in Part II of the present paper. When the inner ventricular layers are inactivated, as in pure subendocardial infarction, normal R or Rs waves occur over the ventricle. When the outer layers are inactivated, as in the preceding experiments, coronary QS or QR waves may occur. Destruction of the outer ventricular layers thus is suffificient to yield markedly abnormal electrocardiograms even though the inner layers remain intact.

Epicardial Heating. The preceding experiments demonstrate that replacement of the normal epicardial R waves with QS waves can be accomplished by damaging the outer ventricular layers. A similar electrocardiographic change was produced fortuitously in two animals during cinematographic study of the heart. In one animal with a pure subendocardial infarct multiple leads from the uninfarcted epicardium over the lesion presented R or Rs waves before cinematographs were taken. These complexes appeared normal except in one or two leads which showed R waves of reduced amplitude. Upon completion of the electrocardiographic exploration high speed cinematographs of the ventricle were recorded under intense illumination. A second set of epicardial tracings was then made from the same lead-points used in the

AMERICAN JOURNAL OF MEDICINE

initial exploration. In contrast to the initial tracings which showed R or Rs waves, the tracings made after the cinematographs presented QS waves in all but a few leads. Histologic examination revealed necrosis and fibrosis involving the inner two-thirds of the ventricular wall. The outer layers were uninfarcted but appeared histologically altered, exhibiting some loss of striae and pyknotic nuclei. In another animal with a transmural infarct R waves were recorded in epicardial leads over a subendocardial extension of the lesion. Cinematographs were then made. After cinematography, the same leads presented pure QS waves.

Since the inner ventricular layers were infarcted in these two animals the epicardial R waves recorded before the cinematographs must have resulted from activation of the outer layers. Replacement of the R waves by QS waves during the experiment was attributed to heating of the outer ventricular layers by the lights used for cinematography. In uninfarcted hearts, however, the cinematographic procedure has been found to cause little or no alteration of the depolarization complex. Hence the live muscle over the subendocardial infarcts must have been somewhat altered before the cinematographs were taken. When additional trauma was inflicted by heat, the outer layers became unable to maintain significant electrical activity. The epicardial R wave therefore disappeared and was replaced by a negative potential transmitted through the inactive muscle from the underlying cavity.

Replacement of R waves by QS waves also may occur clinically without other symptoms of fresh occlusion in patients with pre-existing infarcts. One such patient was found to present R waves in anterior precordial leads after a typical coronary artery occlusion associated with severe pain. The R waves persisted for several months, then suddenly were replaced by QS waves although the patient experienced only vague substernal pain. None of the severe symptoms of the original occlusion were present when the R waves disappeared. As in the experiments, it seems probable that the original occlusion caused a subendocardial infarct with less severe damage to the outer ventricular layers. R waves presumably occurred over the subendocardial infarct, then disappeared several months after occlusion when the electrical activity of the damaged outer layers finally ceased. Thus the sudden development of QS waves in patients without symptoms of fresh occlusion may suggest that pre-existing sub-epicardial damage, probably over a subendocardial infarct, has become intensified.

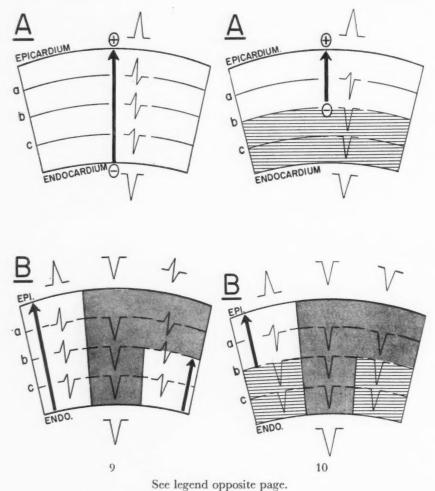
COMMENTS

According to classic electrocardiographic theory, a QS complex recorded in a direct lead from the surface of the left ventricle results from complete through-and-through infarction of the underlying wall. This theory may be explained with reference to the simplified diagram of ventricular depolarization shown in Figures 9A and B. Depolarization is represented as a dipole front advancing at a constant, measurable rate from endocardium to epicardium. Since the positive pole precedes the negative pole, all intramural muscle should lie in the positive field until it is reached by the advancing dipole front. All levels of the wall thus would present an initial positive potential (R wave) which would become progressively greater from the endocardial to the epicardial layers. Consequently, complete through-and-through myocardial death would be necessary entirely to abolish positive potentials within the wall. If only one-half the thickness of the wall were destroyed (Fig. 9B), the epicardial complex should present an R wave one-half of normal size; this deflection would resemble the positive component of the complex along line b in Figure 9A. Similarly. if muscle death were limited to one-fourth or three-fourths of the thickness of the wall the epicardial lead would show an R wave resembling that in the complexes along lines a and c, respectively, in Figure 9A. Only in the event of through-and-through infarction would the epicardial complex be purely negative, like the cavity complex. Clinically as well, a precordial QS wave is the sine qua non of through-andthrough muscle death, with a correspondingly grave prognosis.

Contrary to prevailing theory, it has been observed that subendocardial infarcts involving more than half the thickness of the wall do not alter the electrocardiogram. Furthermore, the data reported in Part I of the present paper show that coronary QS waves may appear over regions of the ventricle which are not completely dead. The persistence of live muscle within the regions was demonstrated by histologic examination, by the presence of injury currents and by the occurrence of systolic contractions. Moreover, the epicardial QS waves usually were not

identical in timing and configuration with the complexes recorded from the underlying cavity or wall. Hence these mural-type epicardial QS waves, unlike cavity-type QS waves, do not result from unaltered transmission of the cavity potential to the epicardium.

is that, because of interference with local blood supply, the tissues immediately surrounding the lesion appeared histologically alive but were electrically altered. The extent of the infarct, under such circumstances, would be greater electrocardiographically than anatomi-



erved with respect to coronary cally. H

As previously observed with respect to coronary QS waves, 5 a mixture of live and dead muscle in the outer ventricular layers was associated with mural-type coronary QS waves. In all seventeen instances the presence of live muscle directly under or near the electrode was established by elevation of the S-T segment, indicating injury current when pressure was applied to the epicardium. In fourteen instances dead as well as live muscle directly under the electrode was seen histologically. The remaining three mural-type QS waves appeared over regions of uninfarcted but histologically altered muscle immediately adjacent to transmural lesions. The precise manner in which the infarct influenced the tracing in these instances must of necessity be a subject of speculation. A reasonable explanation

cally. Hence the three regions of live muscle which yielded mural-type QS waves may have been partially inactivated.

The occurrence of QS waves over regions containing live muscle may be explained by modifying classic electrophysiologic theory to accord with the experimental data reviewed in Part II. Figure 10A and B represents a revision of the theory illustrated in Figure 9, incorporating the concept that the inner ventricular layers are electrocardiographically silent. The shaded area beneath the broken line lies within the silent zone; that is, depolarization of this area does not appear to yield recordable potentials. From a practical viewpoint, therefore, the heavy arrow representing the course of the dipole associated with depolarization of the left ventricle

AMERICAN JOURNAL OF MEDICINE

may be shown to start in the mid-ventricular layers rather than at the endocardial surface. Like the cavity, the inner layers yield pure negative deflections (QS waves) as they face the negative side of the dipole throughout depolarization. Only the outer (unshaded) area presents an initial positive potential which increases as the distance from the epicardium decreases. Destruction of the outer one-half of the wall thus would entirely eliminate the epicardial R wave. Despite the presence of normal muscle through-

out the inner layers, the epicardial lead would show a pure QS wave similar to that recorded along line b. This was demonstrated experimentally in those instances which yielded QS waves after the outer ventricular layers were excised or destroyed.

According to the hypothesis illustrated in Figure 10, QS waves identical with the cavity complex would appear over regions of the ventricle containing live muscle provided that the outer layers were completely dead. This

Fig. 9. A, diagram showing classic concept of normal ventricular depolarization. Line b is drawn midway between endocardial and epicardial surfaces of ventricular wall. Lines a and c bisect the outer and inner halves of the wall, respectively. Arrow perpendicular to epicardial surface represents course of activation wave, which is thought to travel from endocardium to epicardium at a constant speed as an advance of dipoles, the positive pole preceding and the negative pole following the activation front. According to this concept of ventricular depolarization, the complexes recorded from the cavity, the epicardium and various levels within the wall should be as shown in the diagram. The ventricular cavity faces the negative side of the dipole as the activation front proceeds from endocardium to epicardium. Hence it yields a purely negative complex, or QS wave. Conversely, the epicardium yields a purely positive complex, or R wave, as it faces the positive side of the dipole during the entire period of mural activation. All muscle between the endocardium and epicardium faces the positive side of the dipole as activation begins at the endocardium. All the intramural complexes therefore begin with positive deflections. The positive deflection ends when the activation front reaches the electrode, after which a negative component is recorded. Thus the complexes along lines c, b and a become negative as the activation front reaches c, b and a, respectively.

B, diagram showing classic concept of genesis of coronary QS wave. Infarcted muscle is shaded. Left-hand third of diagram represents region of normal muscle. Complexes are therefore the same as in Figure 9A. As activation proceeds from endocardium to epicardium, pure QS wave is recorded in cavity and pure R wave at epicardial surface. Center third of diagram represents region of through-and-through infarction. According to classic theory, cavity negativity is transmitted through the dead muscle to the epicardial surface. Hence the complexes recorded within and over the infarct consist of coronary QS waves identical with the cavity complex. Right-hand third of diagram shows hypothetic infarct involving only the outer half of the ventricle. Activation proceeds normally from endocardium to line b. All levels of the wall face the positive side of the dipole as activation begins at the endocardium. The epicardial and intramural complexes therefore begin with positive deflections, as in the normal region at left of diagram. When the activation wave terminates at the border of the infarct, the positive phase of the complexes recorded at and over line b end. The remainder of these complexes consists of a negative deflection resulting from transmission of cavity negativity. Hence the epicardial complex is an RS wave. Conversely, if only the inner layers of the ventricle were infarcted, the cavity negativity should be transmitted to the epicardium until the activation wave reached the uninfarcted outer layers. Activation of these layers would then proceed toward the epicardium as in the normal region, causing a positive epicardial deflection after the initial negative phase. The complex recorded over the subendocardial infarct would therefore be a QS wave. It is thus apparent that biphasic complexes theoretically would occur over the lesion whether the inner or the outer layers remained uninfarcted. Only through-and-through infarcts would yield coronary QS waves.

Fig. 10. A, diagram showing revised concept of normal ventricular depolarization. Activation of inner layers (lined) is "electrocardiographically silent," presumably because it occurs too rapidly to affect the electrocardiogram. The advance of dipoles associated with ventricular depolarization is not recorded until the activation wave reaches the outer (unlined) layers. In contrast to Figure 9A, therefore, the arrow representing the course of activation extends only from midventricular levels to the epicardial surface. As activation proceeds through the outer ventricular layers toward the epicardium, the inner layers as well as the cavity face the negative side of the dipole. Pure QS waves thus are recorded along lines c and d as well as in the cavity. The intramural complex along line d is a biphasic; it consists of a positive deflection registered as the activation wave travels toward line d, followed by a negative deflection inscribed during activation of muscle between line d and the epicardium. As in Figure 9A, the epicardium faces the positive side of the dipole during the entire period of mural activation and therefore yields an R wave.

B, diagram showing revised concept of genesis of coronary QS wave. Activation of region of normal muscle (left-hand third of diagram) yields QS wave in cavity and R wave on epicardium as in Figure 10A. Cavity negativity is transmitted to epicardium through region of through-and-through infarction (center of diagram), causing a coronary QS wave. Right-hand third of diagram shows hypothetic infarct involving only the outer ventricular layers. In contrast to Figure 9B, activation of the inner layers is electrocardiographically silent. This region is therefore electrocardiographically similar to the adjacent region of through-and-through infarction. Cavity negativity is transmitted through the viable but electrically silent inner layers and through the infarcted outer layers to the epicardium. Coronary QS waves thus occur over the lesion even though the inner layers remain normal. If the outer layers are entirely devoid of live muscle, the coronary QS wave will be identical with the cavity complex. If some live muscle remains in the outer layers, activation of these layers will cause some positivity at the epicardium which would modify the appearance of the coronary QS wave.

situation seldom or perhaps never occurs following coronary artery occlusion because the extent of the infarct generally is greater in the inner ventricular layers than in the outer layers. Hence the coronary QS waves recorded in the present study over regions containing live muscle usually differed from the cavity QS wave. These mural-type QS complexes presumably represent a combination of two potentials: a purely negative potential transmitted to the epicardium from the inner ventricular layers through dead or inactive muscle in the outer layers; and a positive epicardial potential resulting from depolarization of remnants of live muscle in the outer layers. The positive potential modifies the appearance of the QS wave but is not of sufficient magnitude to produce slurs, notches or r waves; that is, it is "buried" in the QS. If the positive potential is somewhat greater, it may cause slurs or notches on the QS wave or small r waves. Patchy infarcts involving the outer ventricular layers thus may yield a variety of abnormal complexes, including muraltype QS waves, QR waves and small r or rS waves, depending on the proportion of live and dead muscle, the location of the lesion and its relationship to the recording electrode.5 This hypothesis accounts for the observation that such complexes occurred over the sixty-eight infarcts in the present study only when both live and dead muscle were in the outer layers of the heart.

High speed cinematographs of the ventricle were recorded simultaneously with direct epicardial leads from over thirty dogs during and after coronary artery ligation. This technic provides an excellent method for correlating electrocardiographic changes with changes in mechanical activity. In general, chronic infarcts from which highly abnormal tracings were obtained exhibited marked impairment of contractility. All cavity-type and most mural-type OS waves thus occurred over regions which ballooned throughout systole. On the other hand, most abnormally small R waves and OR waves as well as a few mural-type QS waves occurred over regions showing various degrees of contractility. Some of these regions shrank markedly during systole, indicating that they underwent strong contraction. Other regions ballooned moderately or irregularly, or they contracted early in systole and ballooned later. Contraction sometimes was strong enough to prevent ballooning but too weak to cause shrinkage. Acute injuries produced by coronary artery ligation, unlike chronic infarcts, always appeared non-contractile. The injured regions ballooned markedly immediately after the coronary artery was tied. Epicardial leads from the ballooning injuries, in contrast to those from ballooning chronic infarcts, never presented Q waves or abnormally small R waves. Instead, they usually contained abnormally large R waves. ¹² Thus in the acute stage of infarction, abnormally large R waves were associated with non-contractility. In the chronic stages QS waves usually were associated with non-contractility but occasionally appeared over partially contractile muscle.

The observations reported in this and the preceding paper indicate that coronary QS waves may be of two types: "Cavity-type" QS waves which appear over regions of through-andthrough infarction, and "mural-type" QS waves recorded over regions containing live muscle at various levels with significant amounts of dead muscle in the outer ventricular layers. Regions yielding cavity-type QS waves consistently failed to contract during ventricular systole and did not give rise to injury currents when traumatized. Regions yielding mural-type QS waves, in contrast, showed contractility in several instances and always presented injury currents in some leads. Thus these two types of coronary QS waves may represent different physiologic as well as pathologic conditions in the ventricle and therefore may differ greatly with respect to

Since mural-type QS waves occurred in the present series of experiments as frequently as cavity-type QS waves, they may also appear commonly in patients with coronary artery disease. Under such circumstances the clinical finding of coronary QS waves would not necessarily establish that the cardiac region yielding these complexes is totally destroyed. A previous study of subendocardial infarction revealed that precordial and limb leads may appear normal although a large proportion of the ventricular myocardium is dead.4 The present observations indicate that these tracings may present abnormal QS waves although the ventricle contains enough live muscle to contract effectively. Thus the importance of considering other signs and symptoms as well as the electrocardiogram in evaluating the condition of the heart is further emphasized.

SUMMARY AND CONCLUSIONS

1. A type of coronary QS wave is described which occurs over regions of the ventricular wall containing significant amounts of live muscle. These deflections, called "mural-type" coronary QS waves, may appear identical with the "cavity-type" QS waves recorded over through-andthrough infarcts. In a series of sixty-eight chronic lesions produced by coronary artery ligation, mural-type QS waves were found as frequently as

cavity-type QS waves.

2. Pathologic and electrocardiographic findings in seventeen regions yielding mural-type QS waves are presented. Histologically, the seventeen regions consisted of necrotic or fibrotic tissue interspersed with variable amounts of live muscle. Electrocardiographically, the regions differed from through-and-through infarcts in several respects: (1) S-T segment elevation, representing injury currents, occurred in epicardial leads when pressure was applied near the lead-point and in intramural leads when sharptipped electrodes were inserted. This evidence of electrical activity never was found in regions of through-and-through infarction. (2) Differences in timing and/or configuration among the epicardial, intramural and cavity complexes were usually observed in regions yielding muraltype QS waves. Regions of through-and-through infarction, in contrast, presented identical QS waves at all levels from cavity to epicardium. Thus the mural-type coronary QS wave, unlike cavity-type QS waves, does not result from unaltered transmission of negative cavity potentials through completely dead muscle to the ventricular surface.

3. High-speed cinematographs of regions yielding mural-type QS waves showed ballooning, indicating non-contractility, in most instances. Several of these regions, however, were seen to contract. Through-and-through infarcts, on the other hand, always ballooned. Muraltype QS waves may occur whether the underlying wall has lost its function completely or only

partially.

4. The outer layers of the left ventricle were damaged in six animals by injection of formaldehyde, in twenty animals by local application of nitric acid, in two animals by injection of nitric acid and in twelve animals by surgical excision. Pure QS waves, slurred or notched QS waves, QR waves and abnormal rS waves occurred over the damaged subepicardial muscle although the inner layers were entirely normal. These obser-

vations confirm previous studies of subendocardial infarcts and normal ventricles which indicate that the R wave in epicardial leads results from depolarization of the outer ventricular layers. Destruction of the outer layers is sufficient to cause pure QS waves as well as other types of abnormal complexes.

5. The sudden replacement of R waves by QS waves may occur without fresh occlusion when the outer ventricular layers previously have been damaged but not infarcted. This situation is most likely to exist in patients with subendocardial infarcts. The R waves persist as long as the subepicardium over the infarct is able to depolarize. When the damaged outer layers become incapable of further electrical activity, the R waves are replaced by QS waves.

6. Diagrams illustrating the genesis of muraltype QS waves are presented. Depolarization of the inner ventricular layers is shown to have no effect on the electrocardiogram. If the outer layers are completely destroyed, QS waves identical with the cavity complex appear over the ventricle despite the presence of normal subendocardial muscle. If the outer layers are partially destroyed, a variety of abnormal complexes, including mural-type QS waves, QR waves and rS waves, occur. This hypothesis is contrasted with classic theory concerning the genesis of normal and abnormal electrocardiograms.

7. No constant relationship exists between changes in the depolarization complex and changes in ventricular contractility following coronary artery ligation. Abnormally large R waves usually occur over non-contractile muscle during the stage of acute injury immediately after the coronary artery is tied. QS waves sometimes occur over contractile muscle during

the stage of chronic infarction.

8. Clinical applications of the experimental findings are discussed. The QS waves recorded from patients with coronary artery disease may not indicate through-and-through infarction in all cases. These deflections also occur when the underlying wall contains enough live muscle to produce injury currents and to contract effectively. In many patients, therefore, coronary QS waves may represent less grave myocardial damage than previously supposed. Other signs and symptoms as well as the electrocardiogram must be considered in evaluating the condition of the heart.

REFERENCES

- PRINZMETAL, M., KENNAMER, R. and MAXWELL, M. Studies on the mechanism of ventricular activity. VIII. The genesis of the coronary QS wave in through-and-through infarction. Am. J. Med., 17: 610, 1954.
- WILSON, F. N., ROSENBAUM, F. R. and JOHNSTON, F. D. Interpretation of the ventricular complex of the electrocardiogram. Advances Int. Med., 2: 1, 1947.
- PRINZMETAL, M., KENNAMER, R., SHAW, C. McK., KIMURA, N., LINDGREN, I. and GOLDMAN, A. Intramural depolarization potentials in myocardial infarction; preliminary report. Circulation, 7: 1, 1953.
- PRINZMETAL, M., SHAW, C. MCK., MAXWELL, M. H., FLAMM, E. J., GOLDMAN, A., KIMURA, N., RAKITA, L., BORDUAS, J. L., ROTHMAN, S. and KENNAMER, R. Studies on the mechanism of ventricular activity. VI. The depolarization complex in pure subendocardial infarction; role of the subendocardial region in the normal electrocardiogram. Am. J. Med., 16: 469-489, 1954.
- SHAW, C. MCK., GOLDMAN, A., KENNAMER, R., KIMURA, N., LINDGREN, I., MAXWELL, M. H. and PRINZMETAL, M. Studies on the mechanism of ventricular activity. VII. The origin of the coronary QR wave. Am. J. Med., 16: 490-503, 1954.
- 6. WILSON, F. N., JOHNSTON, F. D. and HILL, I. G. W.

- Interpretation of the galvanometric curves obtained when one electrode is distant from the heart and the other near or in contact with the ventricular surface. II. Observations on the mammalian heart. *Am. Heart J.*, 10: 176, 1934.
- ROTHMAN, S., RAKITA, L., BORDUAS, J. L. and PRINZMETAL, M. Studies on the mechanism of ventricular activity. XIII. Genesis of the depolarization complex in the mammalian ventricle. Am. J. Physiol., 1954.
- Bellet, S. and Johnston, C. G. The effect of coronary occlusion upon the initial phase of the ventricular complex in precordial leads. J. Clin. Investigation, 13: 725, 1934.
- PARDEE, H. E. B. and GOLDENBERG, M. Electrocardiographic features of myocardial infarction as affected by involvement of the septum and by complete and incomplete transmural involvement. Am. Heart J., 30: 367, 1945.
- DURRER, D., TWEEL, L. H. and BLECKMAN, J. R. The spread of the activation in the left ventricular wall of the dog. Reprinted from Proceedings, Series C, No. 2, 1953, K. Nederl. Akademie. Van Wetenschappen, Amsterdam.
- 11. Sodi-Pallares, D. Personal communication.
- RAKITA, L., BORDUAS, J.-L., ROTHMAN, S. and PRINZMETAL, M. Studies on the mechanism of ventricular activity. Early RS-T segment and QRS changes following experimental coronary artery occlusion. Am. Heart J., 1954.

The Value of Rauwolfia Serpentina in the Hypertensive Patient*

FRANK A. FINNERTY, JR., M.D. †

URING the past two years Rauwolfia serpentina has come to be widely used in this country in the management of hypertension. Published reports 1-3 indicate that it is moderately hypotensive, that it slows the pulse, exerts a mild sedative action and is remarkably free from clinical toxicity. Used alone, Rauwolfia seems to be most effective in excitable patients with tachycardia and hypertension. In these patients relief of the anxiety and tachycardia may be apparent before any consistent change in blood pressure is established. Published reports indicate that when Rauwolfia is used in conjunction with more potent hypotensive agents it relieves or prevents drug-induced side effects and may synergistically potentiate the therapeutic actions. 4,5

Several practical questions remain unanswered, however. This study was undertaken in an attempt to furnish answers to the following:

1. Is Rauwolfia therapy superior to simple sedation in the management of the milder forms of hypertension?

2. Does Rauwolfia when used alone produce a significant reversal in organic changes, e.g., decrease in heart size or regression of retinopathy?

3. Does the addition of Rauwolfia produce a significant reduction in dosage requirements of Veratrum viride? Are the side actions of Veratrum viride reduced?

4. Can Rauwolfia be substituted for hydralazine in patients who are on a hexamethonium-hydralazine regimen? Does the addition of Rauwolfia allow a significant reduction in dosage requirements of either or both drugs?

METHODS AND MATERIALS

The patients in this study were from the Hypertensive Clinic at Georgetown University Medical Center, the medical wards and clinics of the Georgetown Medical Division of the District of Columbia General Hospital, and U. S. Army Dispensary, The Pentagon, and from the author's private practice. All had undergone the routine clinical and laboratory studies which are ordinarily used to evaluate the hypertensive state, including a complete history and physical examination, urinalysis, fractional phenolsulfonphthalein test, blood urea nitrogen determination, electrocardiogram and chest x-ray.

There are three therapeutic groups in this series of eighty-nine patients. The first comprises forty-four patients who received Rauwolfia (rauwiloid®‡) as the sole therapeutic agent. The second group, twenty-two patients, had previously been maintained with Veratrum (veriloid®§) alone and have been changed to combined therapy with rauwiloid and veriloid. The third group consists of twenty-one patients who had been receiving ganglionic blocking agents (hexamethonium or pentapyrrolidinium) and/or hydralazine (apresoline®||) before the addition of rauwiloid. All of the patients were ambulatory.

In the first group, before rauwiloid therapy was instituted, all the patients had been treated with phenobarbital, 0.1 gm./day, or amytal sodium, 0.2 gm./day, for at least six weeks. Blood pressures were recorded at least once weekly throughout the study. Rauwolfia¶ was

‡ Rauwiloid (an alkaloidal extract from Rauwolfia serpentina) used in these studies was supplied by the Riker Laboratories, Los Angeles, Calif.

§ Veriloid (an alkaloidal extract of Veratrum viride) used in these studies was supplied by the Riker Laboratories, Los Angeles, Calif.

Appresoline used in these studies was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J.

¶ Early in the study, tablets of crude Rauwolfia

serpentina were used and dosages were expressed in

* From the Department of Medicine, Georgetown University School of Medicine and the Georgetown University Medical Division, District of Columbia General Hospital. This investigation was supported by research grants from Ciba Pharmaceutical Products, Inc., Summit, N. J., Irwin Neisler & Co., Decatur, Ill., and Riker Laboratories, Inc., Los Angeles, Calif. The opinions expressed by the author in this paper are his own and do not necessarily reflect the views of the Medical Department of the U. S. Army.

† Present address: U. S. Army Dispensary, The Pentagon, Washington, D. C.

given in doses of 250 mg, twice daily when the experimental drug was used and 4 mg, at bed-time when rauwiloid was used. Placebos were substituted at least once during the study in all

patients, for a six-week period.

The second group of patients had been receiving veriloid for at least five months before Rauwolfia was added, the average duration of therapy being 9.5 months. The dose of veriloid varied from 10 to 29 mg./day with an average of 18 mg./day. In order to determine the least amount of Veratrum required for optimal results, during the month before rauwiloid was added, the veriloid dosage was reduced by increments until a definite rise in the arterial pressure occurred. The dosage of rauwiloid was the same as in the first group.

Twenty-one patients were included in the third group. Fourteen of these, who have been followed up for more than a year, have been receiving hexamethonium by injection twice daily in dosages ranging between 100 to 400 mg./day, plus apresoline orally in daily doses varying between 100 to 700 mg. Seven patients, followed up for more than a year, had been taking hexamethonium orally in daily dosages ranging between 1 and 5 gm., and apresoline in daily dosages varying between 200 and 800 mg. As in the veriloid group, a month before the addition of Rauwolfia the doses of hexamethonium and apresoline were lowered in an incremental fashion until a rise in arterial pressure occurred. When the dosage requirements of the two hypotensive agents were found, Rauwiloid was added in dosage of 4 mg. at bedtime.

Two patients (one a malignant hypertensive and the other with grade II retinopathy) had received oral pentapyrrolidinium (ansolysin*) therapy for three months before rauwiloid was added. Both of these patients have now been followed up for six months or longer. Initial dosage of ansolysin was 22.5 mg., three times a day, increased slowly to 200 to 300 mg. per day.

RESULTS

Rauwiloid. Forty-four patients received rauwiloid as the sole hypotensive agent for periods of five months to two years, with an average duration of nine months. Twenty-four patients had grade II hypertensive retinopathy; of these twenty also presented congestive heart failure. Twenty patients had normal or grade I fundi.

In the twenty patients with normal or grade I fundi there was an average reduction of 20.0 mm. Hg in systolic pressure and an average reduction of 18.2 mm. Hg in diastolic pressure. Twelve of the twenty patients (60 per cent) showed more than 20 mm. Hg reduction in diastolic pressure, and an additional four of the twenty patients (20 per cent) showed more than a 10 mm. Hg reduction in diastolic pressure. The average fall of all twenty was from 150/110, optimum, while on sedation, to an average of 135/95 on rauwiloid. The level of arterial pressure in both these groups returned to pretreatment levels when placebos were substituted. The heart rate was slowed an average of 9.7 beats per minute. Four of the six patients with normal fundi showed no objective response to the therapy.

In the twenty-four patients with grade II retinopathy there was an average reduction of 13.3 mm. Hg in systolic pressure, and an average reduction of 9.7 mm. Hg in diastolic pressure from the pretreatment average of 165/115. Nine patients (36 per cent) showed a greater than 15 mm. Hg in diastolic pressure with a return of the blood pressure to pretreatment levels when

placebos were substituted.

The heart rate was reduced an average of 8 beats per minute, with a range of 0 to 20 beats per minute. Headache, which was present in seventeen of the twenty-four patients before therapy, was alleviated in sixteen. The severity of the congestive heart failure remained unchanged. The fifteen patients whose blood pressure did not fall significantly showed no objective benefit from Rauwolfia therapy but reported subjective improvement, notably relief of headache.

The hypotensive and bradycrotic action of Rauwolfia in the dosage used did not become manifest for from ten days to two weeks. The full hypotensive effect frequently was not achieved until after three to four months of therapy. Similarly, when medication was discontinued and placebos were substituted, the arterial pressure frequently did not show an appreciable increase for from three to four weeks. Our experience indicates that there is little advantage to giving the medication more than once daily. Twelve patients of the forty-four

terms of crude root content. Our present routine is to use the alkaloidal extract, rauwiloid, and dosages are expressed in terms of milligrams of alkaloids.

* Ansolysin used in these studies was supplied by May and Baker, Ltd., London, England.

AMERICAN JOURNAL OF MEDICINE

showed a transient fall in arterial pressure during the first month of therapy but returned toward pretreatment levels a few weeks later. For these patients addition of a more potent agent was required. Increasing the dosage did not enhance the therapeutic effect or prolong the hypotensive effect in this group.

There are certain interesting findings in addition to the hypotension response to rauwiloid. Forty of the forty-four patients gained an average of 5 pounds during the first three months of therapy, with a range of 0 to 12 pounds. This represented a true weight gain, was not due to the development of edema and was proportionate to an increased appetite and general feeling of well-being.

Thirty patients slept more soundly and twentyfive complained of fatigue on arising which lasted from one-half to one hour. There was relief of headache in sixteen of seventeen patients and relief of anxiety in sixteen patients.

Mild nasal stuffiness was noted in fifteen patients. Slightly loose stools were noted in ten and mild abdominal cramping was noted on one or more occasions in fifteen patients.

Restless nights with nightmares were a complaint in three patients. This symptom was alleviated by reducing the Rauwolfia dosage by half. Five patients noted a transitory giddy feeling, as though they were momentarily "out of contact." One patient noted a maculopapular rash which disappeared when medication was withheld and which did not return when medication was again instituted. No serious toxic effects have been noted from rauwiloid. (Table I.)

Rauwiloid and Veriloid. There were twenty-two patients in this group, including eighteen with grade II fundal changes, two with grade III retinopathy and two patients with malignant hypertension. The duration of combined therapy up to the time of this report varied from five to sixteen months, with an average of 8.5 months. (Table II.)

With the addition of rauwiloid it was possible to reduce the daily veriloid dosage by one-half or more in seven cases, by one-third in five cases, and by one-fifth in one case. The dosage of veriloid could not be reduced in nine cases. The average optimum blood pressure on veriloid alone was 160/115. Upon the addition of rauwiloid the average reduction in blood pressure below that obtained with veriloid alone was 8.9 mm. Hg systolic and 6.8 mm. Hg diastolic despite the

lower dosage of veriloid. The average additional reduction in pulse rate was 6.4.

The incidence of nausea and vomiting in the patients taking veriloid alone varied between twice a week and once every two weeks. When amytal® sodium was added (60 mg., three times daily), the incidence of vomiting varied between once every ten days to once a month. With the reduced dosage of veriloid plus rauwiloid, plus amytal sodium, ten of the twenty-two patients, or ten of the thirteen patients who benefited blood pressure-wise, have noted no nausea or vomiting in six months. Two patients who previously had experienced vomiting once weekly on veriloid alone had emesis only once a month upon combined therapy. Although rauwiloid did not reduce the veriloid dosage in two patients, it did reduce the incidence of emesis by three-fourths.

Sixteen of the twenty-two patients (73 per cent) were clearly benefited by the addition of rauwiloid to veriloid, as manifested either by a reduction in blood pressure or reduction in the incidence of nausea and vomiting or, most commonly, a reduction in both. The six patients who did not respond to the addition of rauwiloid include two patients in the malignant phase and four patients with severe grade II hypertensive cardiovascular disease. Ganglionic blocking agents were needed to control the hypertension in these patients.

Hexamethonium and Apresoline plus Rauwiloid. Twenty-one patients were in this group, including six patients with grade IV retinopathy (Keith-Wagener), four with grade III retinopathy and eleven patients with grade II retinopathy (five of these patients were in congestive heart failure). The average blood pressure for the whole group while on optimum dosage of hexamethonium was 175/120. (Table III.)

This group is further subdivided as follows: (1) fourteen patients who had been taking parenteral hexamethonium and oral apresoline, and (2) seven patients who had been taking oral hexamethonium and oral apresoline. After addition of rauwiloid the following change in therapy was possible without loss of hypotensive effect: It was possible to omit 200 mg. of apresoline and reduce the parenteral dose of hexamethonium by one-half in four patients; 100 mg. of apresoline were omitted in three patients; the dose of parenteral hexamethonium was reduced by one-half in two patients; 200 mg. of apresoline were omitted and the parenteral hexamethonium dosage was reduced by

TABLE I

			1 ABLE	2 1		
Patient and Grade of Hypertension	Drug	Dura- tion in Months	Reduction in Blood Pressure below Optimum Barbiturate Level (mm. Hg)	Reduction in Pulse Rate below Optimum Barbiturate Level (Beats/min.)	Toxicity	Remarks
J. M., w., m., 40* Normal fundi	Rauwiloid	6	30/20	10	Fatigue in A.M.	Relief of anxiety; slept more soundly
J. T., w., m., 36 Normal fundi	Rauwiloid	5	10/20	6	Stuffy nose, fatigue in A.M.	Relief of anxiety; slept more soundly
J. W., w., m., 36 Normal fundi	Rauwiloid	6	None	5	Fatigue in A.M.	Begun on veriloid with no response in 3 mo.
B. G., w., m., 40 Normal fundi	Rauwiloid	6	None	0	Fatigue in A.M.	Slept more soundly; decrease in headache
B. H., w., m., 41 Normal fundi	Rauwiloid	8	None	0	Mild abdominal cramping	Sleeps better; decrease in head- ache; less anxiety
M. R., w., m., 39 Normal fundi	Rauwiloid	8	None	0	Fatigue in A.M.	No response
M. J., w., f., 41 Grade I	Rauwiloid	24	20/30	20	Stuffy nose, abdominal cramps	Relief of anxiety and headache; slept more soundly
C. H., w., m., 37 Grade 1	Rauwiloid	5	30/20	15	Giddy feeling	Relief of anxiety; slept more soundly
C. A., w., m., 49 Grade 1	Rauwiloid	8	30/20	15	Tired in A.M.	Relief of headache; slept more soundly
C. N., w., m., 41 Grade 1	Rauwiloid	8	30/20	10	Stuffy nose, abdominal cramps	Slept more soundly
M. F., w., m., 36 Grade 1	Rauwiloid	5	10/20	10	Fatigue in A.M.	Slept more soundly; weight gain
M. H., w., f., 38 Grade 1	Rauwiloid	8	20/20	10	Stuffy nose, fatigue in A.M.	Slept more soundly
B. J., c., f., 43 Grade 1	Rauwiloid	5	40/15	6	Abdominal cramps	Relief of anxiety; slept more soundly
M. F., w., f., 36 Grade I Congestive failure	Rauwiloip	5	20/15	10	Stuffy nose, abdominal cramps	Headache less; slept more soundly
M. O., w., m., 41 Grade 1	Rauwiloid	8	35/30	15	Fatigue in A.M.	Marked increase in appetite
C. A., w., m., 40 Grade 1	Rauwiloid	6	30/20	10	Fatigue in A.M.	Decreased anxiety; slept more soundly
L. B., w., m., 46 Grade 1	Rauwiloid	12	40/45	10	Stools softer; fatigue in A.M., occasional restless nights	Decreased anxiety; slept more soundly; decrease in headache
O. V., w., m., 37 Grade 1	Rauwiloid	7	30/20	15	Fatigue in A.M., stuffy nose	Slept more soundly; decrease in headache
E. P., w., m., 39 Grade 1	Rauwiloid	10	15/20	6	Fatigue in A.M.	Slept more soundly; decrease in headache
C. G., w., m., 34 Grade 1	Rauwiloid	10	20/30	10	Macular rash, stuffy nose	Slept more soundly; decrease in headache
E. M., w., f., 57 Grade II Congestive failure	Rauwiloid	6	30/20	20	Stuffy nose	Relief of anxiety; slept more soundly
F. G., w., m., 35 Grade II	Rauwiloid	5	None	10	Abdominal cramps	Less anxiety; slept more soundly
F. S., c., m., 50 Grade II Congestive failure	Rauwiloid	5	None	None	Stuffy nose, fatigue in A.M.	Relief of headache; slept more soundly

Table 1 (Continued)

Patient and Grade of Hypertension	Drug	Dura- tion in Months	Barbiturate Level (mm. Hg)	Reduction in Pulse Rate below Optimum Barbiturate Level (Beats/min.)	Toxicity	Remarks
M. W., c., f., 56 Grade II Congestive failure	Rauwiloid	5	30/20	10	Stuffy nose, fatigue in A.M.	No relief of headache; slept more soundly
L. S., c., m., 59 Grade II Congestive failure	Rauwiloid	6	10/0	10	Stuffy nose, fatigue in A.M.	Relief of headache; slept more soundly
A. L., c., f., 58 Grade II Congestive failure	Rauwiloid	5	0/10	10	Abdominal cramps, fatigue in A.M.	Relief of headache; slept more soundly
E. H., c., f., 29 Grade II Congestive failure	Rauwiloid	5	50/15	10	Fatigue in A.M.	Relief of headache; slept more soundly
J. W., c., m., 48 Grade 11 Congestive failure	Rauwiloid	10	10/30	10	Abdominal cramps, diarrhea	Headache less; no change in failure; anxiety relieved
J. W., c., m., 61 Grade II Congestive failure	Rauwiloid	10	30/20	10	abdominal cramps	No change in failure; less anxiety
R. W., c., f., 58 Grade 11 Congestive failure	Rauwiloid	6	None	5	Fatigue in A.M.	Decrease in headache; no change in failure
J. M., c., m., 33 Grade II Congestive failure	Rauwiloid	6	10/10	5	Fatigue in A.M.	No change in heart failure; anxiety less
E. B., c., f., 50 Grade II Congestive failure	Rauwiloid	24	None	4	Stuffy nose, abdominal cramps	Headaches less; sleeps better; less anxiety; no change in failure
R. B., w., m., 40 Grade II Congestive failure	Rauwiloid	12	20/20	10	Fatigue in A.M.	Less anxiety; euphoria; no change in failure
E. T., c., m., 60 Grade 11 Congestive failure	Rauwiloid	7	40/20	6	Stuffy nose, abdominal cramps	Euphoria; headaches less
E. G., w., m., 36 Grade II Congestive failure	Rauwiloid	8	None	4	Fatigue in A.M.	No response
F. A., w., m., 50 Grade II	Rauwiloid	7	None	6	Abdominal cramps	Euphoria
G. S., c., m., 54 Grade 11 Congestive failure	Rauwiloid	9	10/20	6	Fatigue in A.M.	Less anxiety; slept more soundly
T. B., c., f., 50 Grade II Congestive failure	Rauwiloid	8	None	10	Stuffy nose, abdominal cramps	Decreased headache; slept more soundly
J. M., c., m., 33 Grade II Congestive failure	Rauwiloid	8	None	4	Abdominal cramps	No response
B. R., w., m., 40 Grade II Congestive failure	Rauwiloid	7	10/10	10	Stuffy nose, abdominal cramps	Less anxiety; slept more soundly
L. V., w., m., 39 Grade 11 Congestive failure	Rauwiloid	7	20/20	6	Fatigue in A.M., stuffy nose	Less anxiety
C. C., w., m., 45 Grade 11	Rauwiloid	6	None	6	Abdominal cramps	Feels better; less anxiety
B. W., c., m., 60 Grade 11	Rauwiloid	5	None	0	Nightmares, stuffy nose	No response
H. W., c., m., 49 Grade II Congestive failure	Rauwiloid	8	30/20	10	Fatigue in A.M., stuffy nose, abdominal cramps	No change in failure; slept more soundly; less anxiety

^{*} w = white; c = colored; m = male; f = female.

TABLE II

	TABLE II								
Patient and Grade of Hypertension	Medication per Day	Duration in Months	Blood Pressure* (mm. Hg)	Pulse (Beats/min.)	Remarks				
M. L., c., f., 34† Grade II	Veriloid 10 mg.	24	170 110	78	Vomiting 1–2x/wk.				
	Veriloid 6 mg. + rauwiloid	12	$\frac{150}{100}$	60	No vomiting in 6 mo.				
R. T., w., m., 46 Grade 11	Veriloid 29 mg.	24	190 125	72	Vomiting every 10 days				
	Veriloid 14 mg. + rauwiloid	12	$\frac{160}{110}$	68	No vomiting in 6 mo.				
D. M., w., m., 39 Grade 11	Veriloid 24 mg.	6	$\frac{170}{120}$	76	Vomiting twice a month.				
	Veriloid 12 mg. + rauwiloid	6	$\frac{160}{110}$	70	No vomiting in 6 mo.				
S. S., w., m., 40 Grade II	Veriloid 25 mg.	36	$\frac{170}{120}$	68	Vomiting twice a month				
	Veriloid 21 mg. + rauwiloid	12	$\frac{150}{110}$	68	No vomiting in 6 mo.				
L. N., w., f., 58 Grade 11	Veriloid 18 mg.	24	$\frac{190}{108}$	80	Vomiting twice monthly				
	Veriloid 18 mg. + rauwiloid	12	170 100	64	No vomiting in 9 mo.				
M. K., w., f., 60 Grade п	Veriloid 20 mg.	12	$\frac{160}{110}$	70	Vomiting once weekly				
F C	Veriloid 6 mg. + rauwiloid	6	140 95	65	Vomiting once every 2 mo.				
E. G., c., m., 60 Group 11	Veriloid 16 mg.	9	190 120 190		Vomiting once weekly				
F P c f 42	Veriloid 12 mg. + rauwiloid Veriloid 15 mg.	16	110 160	80	Vomiting once every 2 mo. Vomiting once weekly				
E. P., c., f., 43 Grade 11	Veriloid 15 mg. +	5	110 160	76	Vomiting once in 3 mo.				
P. H., c., f., 62	rauwiloid Veriloid 13.5 mg.	24	110 190	84	Vomiting once a month				
Grade II	Veriloid 6 mg. +	12	110 190	60	No vomiting in 1 yr.				
V. L., w., f., 33	rauwiloid Veriloid 12.5 mg.	15	100 170	80	Vomiting once every 3 wk.				
Grade II	Veriloid 6 mg. +	6	120 160	65	No vomiting in 6 mo.				
H. C., w., m., 56	rauwiloid Veriloid 18.5 mg.	16	110 180	94	Vomiting once every 2 mo.				
Grade II	Veriloid 18.5 mg. +	12	130 180	94	No vomiting in 1 yr.				
P. H., w., f., 56	rauwiloid Veriloid 16 mg.	8	115 180	80	Vomiting twice a month				
Grade II	Veriloid 18 mg. +	6	120 170 110	70	No vomiting in 6 mo.				
С. W., с., f., 41 Grade и	Veriloid 22 mg.	24	110 180 115	84	Vomiting once every 2 wk.				
Grade II	Veriloid 18 mg. +	6	180 115	78	Vomiting once a month				

TABLE II (Continued)

Patient and Grade of Hypertension	Medication per Day	Duration in Months	Blood Pressure* (mm. Hg)	Pulse (Beats/min.)	Remarks
A. V., w., m., 45 Grade II	Veriloid 21 mg.	5	160 120	82	Vomiting once weekly
	Veriloid 21 mg. + rauwiloid	5	$\frac{160}{120}$	82	No effect from addition of rauwiloid
С. O'N., w., m., 64 Grade II	Veriloid 20 mg.	6	$\frac{210}{120}$	88	Vomiting once every 2 wk.
	Veriloid 20 mg. + rauwiloid	5	$\frac{210}{120}$	82	No benefit from addition of rauwiloid
H. G., w., m., 49 Grade и	Veriloid 14 mg.	6	$\frac{150}{120}$	70	Vomiting every 2 wk.
	Veriloid 16 mg. +	7	$\frac{150}{120}$	70	No benefit from addition of rauwiloid
M. B., w., m., 33 Grade п	Veriloid 20 mg.	8	$\frac{180}{125}$	82	
	Veriloid 20 mg. +	6	$\frac{180}{125}$	82	No effect from addition of rauwiloid
P. H., w., f., 56 Grade 11	Veriloid 18 mg.	6	$\frac{170}{110}$	80	Addition of rauwiloid caused no reduction in blood pressure but reduced veriloid dosage
	Veriloid 12 mg. + rauwiloid	6	$\frac{170}{110}$	76	No vomiting in 6 mo.
O. S., w., m., 39 Grade III	Veriloid 22 mg.	6	$\frac{190}{130}$	84	
	Veriloid 28 mg. + rauwiloid	5	$\frac{190}{130}$	84	No effect from addition of rauwiloid
M. W., c., f., 64 Grade 11	Veriloid 16 mg.	10	$\frac{180}{120}$	80	Vomiting once every 2 wk.
	Veriloid 12 mg. + rauwiloid	6	$\frac{160}{110}$	76	Vomiting once every 6 wk.
H. G., w., m., 43 Grade IV	Veriloid 20 mg.	24	$\frac{180}{120}$	80	Vomiting once every 2 wk.
	Veriloid 10 mg. -	7	$\frac{160}{110}$	70	Vomiting once every 2 mo.
F. S., c., m., 41 Grade IV	Veriloid 24 mg.	5	$\frac{190}{140}$	84	Vomiting once every 2 wk. with veriloid
	Veriloid 26 mg. + rauwiloid	5	$\frac{200}{140}$	84	No change with rauwiloid

* Average of many readings.

† w = white; c = colored; m = male; f = female.

two-thirds in three; apresoline (200 mg.) was omitted and the dose of hexamethonium was reduced by 50 mg. in one; and 200 mg. of apresoline were omitted in one case. Two patients (one with malignant hypertension and one with grade III retinopathy) showed no beneficial effect from the addition of rauwiloid.

Similar results were obtained when rauwiloid was added to the regimen of patients taking hexamethonium orally. In these patients the

dose of hexamethonium could be reduced by one-third or more in all instances and apresoline could be omitted in all but one patient; in this case it was reduced from 700 to 300 mg. per day.

Thus significant reductions in hexamethonium dosage and omission of apresoline were possible in eighteen of twenty-one patients. The blood pressure remained unchanged in fourteen. In the seven patients in whom a fall in arterial pressure was noted there was an average reduc-

TABLE III

Patient and Grade of Hypertension	Medication per Day	Dura- tion in Months	Pressure* (mm. Hg)	Pulse (Beats/min.)	Remarks
H. W., w., m., 42† Grade II	Oral hexamethonium 4 gm.; apresoline 700 mg.	10	180 110	80	
	Oral hexamethonium 3 gm.; apresoline 400 mg.; rauwiloid 4 mg.	10	$\frac{180}{110}$	72	No constipation or blurring of vision
R. M., w., m., 38 Grade II	Oral hexamethonium 3 gm.; apresoline 400 mg.	8	$\frac{160}{115}$	80	
	Oral hexamethonium 2 gm.; rauwiloid 4 mg.	9	$\frac{150}{105}$	74	Blurring of vision; constipa- tion much improved
P. S., w., m., 32 Grade II	Oral hexamethonium 1 gm.; apresoline 300 mg.	5	$\frac{150}{105}$	80	No toxicity
	Oral hexamethonium 1 gm.; rauwiloid 4 mg.	7	$\frac{150}{100}$	70	No toxicity save 13 pound weight gain
N. A., w., m., 39 Grade II	Oral hexamethonium 4 gm.; apresoline 100 mg.	5	$\frac{190}{125}$	80	
Grade II	Oral hexamethonium 2 gm.; rauwiloid 4 mg.	6	$\frac{160}{110}$	65	Constipation; blurring of vi- sion; fatigue much less
B. B., w., f., 34 Grade II	Oral hexamethonium 4 gm.; apresoline 100 mg.	9	150 105	80	sion, langue muen less
Orace ii	Oral hexamethonium 1 gm.; rauwiloid 4 mg.	6	$\frac{150}{105}$	74	Constipation greatly relieved
P. P., w., m., 33 Grade II	Parenteral hexamethonium 100 mg.; apresoline 200 mg.	12	$\frac{160}{120}$	80	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.		150 100	70	Postural dizziness; constipa- tion; fatigue completely alleviated
T. O., w., m., 44 Grade II	Parenteral hexamethonium 250 mg.; apresoline 200 mg.	12	160 115	78	
	Parenteral hexamethonium 200 mg.; rauwiloid 4 mg.		$\frac{160}{115}$	68	Flushing and tachycardia completely alleviated
P. C., w., m., 45 Grade 11	Parenteral hexamethonium 200 mg.; apresoline 100 mg.	12	$\frac{160}{110}$	78	
	Parenteral hexamethonium 200 mg.; rauwiloid 4 mg.	6	$\frac{160}{110}$	78	Mild blurring of vision eliminated
В. W., с., f., 60 Grade и	Parenteral hexamethonium 300 mg.; apresoline 200 mg.	12	$\frac{160}{110}$	80	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.	7	$\frac{160}{110}$	65	Constipation eliminated
V. F., c., f., 46 Grade II	Parenteral hexamethonium 200 mg.	12	$\frac{170}{110}$	80	
	Parenteral hexamethonium 100 mg.	6	$\frac{170}{110}$	75	Less dizziness
F. H., c., m., 32 Grade 11	Oral hexamethonium 4 gm.; apresoline 200 mg.	6	$\frac{170}{110}$	80	
	Oral hexamethonium 2 gm.; rauwiloid 4 mg.		$\frac{170}{110}$	75	No constipation
W. B., c., m., 46 Grade III	Parenteral hexamethorium 300 mg.; apresoline 200 mg.	9	190 130	85	
	Parenteral hexamethonium 150 mg.; rauwiloid 4 mg.	6	$\frac{190}{120}$	80	Constipation; dizziness less

TABLE III (Continued)

Patient and Grade of Hypertension	Medication per Day	Dura- tion in Months	Pressure * (mm. Hg)	Pulse (Beats/min.)	Remarks
L. S., c., m., 40 Grade III	Parenteral hexamethonium 100 mg.; apresoline 100 mg.	8	200 120	85	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.	8	$\frac{190}{110}$	60	No tachycardia
P. H., c., f., 48 Grade III	Parenteral hexamethonium 400 mg.; apresoline 200 mg.	7	$\frac{180}{130}$	85	
	Parenteral hexamethonium 400 mg.; apresoline 200 mg.; rauwiloid 4 mg.	6	$\frac{180}{130}$	85	No response to addition of rauwiloid
B. H., c., m., 46 Grade III	Oral hexamethonium 3 gm.; apresoline 200 mg.	8	$\frac{160}{105}$	80	
	Oral hexamethonium 2 gm., rauwiloid 4 mg.	7	$\frac{160}{105}$	70	No constipation; less blurring of vision
R. E., c., f., 43 Grade IV	Parenteral hexamethonium 200 mg.	24	180 115	80	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.	12	$\frac{180}{115}$	75	Less abdominal distention and constipation
F. S., c., m., 38 Grade IV	Parenteral hexamethonium 300 mg.; apresoline 200 mg.	6	190 135	80	
	Parenteral hexamethonium 300 mg.; apresoline 200 mg.; rauwiloid 4 mg.	5	$\frac{190}{135}$		Rauwiloid caused no change in blood pressure or toxicity
E. W., c., f., 52 Grade IV	Parenteral hexamethonium 200 mg.; apresoline 200 mg.	12	170 105	80	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.	7	$\frac{170}{105}$	75	No constipation
S. G., c., f., 35 Grade IV	Parenteral hexamethonium 300 mg.; apresoline 200 mg.	6	170 115	80	
	Parenteral hexamethonium 150 mg.; rauwiloid 4 mg.	5	$\frac{170}{115}$	70	Less dizziness; no blurring of vision
F. G., c., f., 50 Grade IV	Parenteral hexamethonium 200 mg.; apresoline 200 mg.	6	$\frac{190}{120}$	80	
	Parenteral hexamethonium 100 mg.; rauwiloid 4 mg.	5	$\frac{190}{120}$	75	Less blurring of vision; less palpitation
R. F., c., m., 46 Grade iv	Parenteral hexamethonium 200 mg.; apresoline 100 mg.	12	$\frac{170}{110}$	80	
	Parenteral hexamethonium 200 mg.; rauwiloid 4 mg.	6	$\frac{150}{90}$	60	Slight constipation eliminated

^{*} Average of many readings. † w = white; c = colored; m = male; f = female.

tion of 11.4 mm. Hg systolic and 13.0 mm. Hg diastolic following the addition of rauwiloid. The pulse rate was reduced in all but three, with an average reduction of 8.7 beats per minute.

The side effects induced by hexamethonium and apresoline, notably constipation, blurring of vision, collapse reactions, tachycardia and headaches, were negligible following the addition of rauwiloid and reduction in dosage or omission of the offending agents.

As the dosage of hexamethonium, in combination with rauwiloid, was determined, these patients were given rauwiloid and hexamethonium in the same tablet* administered after meals and at bedtime. Data on these patients will be the subject of a future report.

In the two patients treated with pentapyrrolidinium, rauwiloid was effective in further reducing the diastolic pressure 10 mm. Hg in each, and decreasing the dosage by 50 mg. in one and 150 mg. in the other. This resulted in greatly reducing the side effects.

COMMENTS

The fact that seventeen of our twenty patients with normal or grade I fundi treated with rauwiloid alone showed an average reduction in arterial pressure of 20 mm. systolic and 18 mm. diastolic below the optimal level obtained with mild sedation, and showed a rise in arterial pressure and a return of anxiety when placebos were substituted, leaves little doubt of the value of the drug in mild hypertensive vascular disease. The symptomatic improvement, particularly the relief of headache, bradycardia, sounder sleep, weight gain and relief of anxiety, although difficult to evaluate in hypertensive patients, was so consistent and frequently so dramatic that it must be mentioned. We agree with Wilkins1 that these symptomatic benefits are quite real and are the most easily identifiable effects of the

In our experience the weight gain may be a problem, particularly in the already obese patient. The patient should be warned of this fairly frequent accompaniment of the drug and his caloric intake may need to be reduced accordingly.

It is of interest that of the six patients with normal fundi, four failed to respond to rauwiloid. This suggests that Rauwolfia, like other and more potent hypotensive agents, is less likely

* Rauwiloid + Hexamethonium, Riker Laboratories, Inc., Los Angeles, Calif.

to produce a good therapeutic response in the absence of demonstrable vascular changes.

Although approximately one-third of the patients with grade II hypertension manifested a reduction of blood pressure and "felt well" while receiving the drug, it should be noted that there was no evidence that the status of their vascular disease was changed appreciably. Congestive failure, present in twenty of these patients, was not benefited in any case. It should be emphasized, therefore, that in the presence of hypertensive cardiovascular disease with congestive failure more potent hypotensive therapy than Rauwolfia alone is indicated. Indeed the physician may do harm in withholding additional therapy even though the patient may be improved symptomatically.

The ability of Veratrum to lower blood pressure has never been questioned, and the recent development of purified well standardized extracts plus intensive clinical and pharmacologic investigations have proved the drug to be a safe and effective hypotensive agent.^{7–11} The only drawback to wide acceptance of the drug has been the relatively narrow margin between the dosage required for hypotension and that causing nausea or vomiting. This has made dosage adjustment difficult and side actions frequent.

Studies by Freis¹⁵ and others have shown that Veratrum is best tolerated after breakfast, midafternoon and at bedtime, and the author¹⁶ has shown that amytal sodium given concurrently with Veratrum tends to reduce nausea and vomiting. Utilizing the three-time daily schedule with amytal sodium, and omitting the intake of fluids and food for four hours after medication, has been successful in reducing the incidence of vomiting from an average of once every ten days to once every twenty-one days.

The addition of Rauwolfia to Veratrum permits the use of lower doses of Veratrum (the dose of veriloid could be reduced by more than one-third in 50 per cent of cases), thus greatly increasing the margin between the therapeutic and emetic dose. It also seems to enhance the hypotensive effect. The addition of rauwiloid makes veriloid easier to administer, more effective and practically does away with unpleasant side reactions. With the reduced dosage of rauwiloid plus amytal sodium, ten of the thirteen patients who showed a reduction in blood pressure have noted no vomiting in six months. Even when the dosage of veriloid could not be reduced by the addition of rauwiloid

AMERICAN JOURNAL OF MEDICINE

a significant decrease in the incidence of vomiting was noted.

Prior to the institution of rauwiloid we found it possible to reduce the veriloid dosage by more than one-third in six patients before the arterial pressure began to return to pretreatment level. Although large doses of Veratrum were needed originally to control the hypertensive state, it became apparent that these large doses were no longer necessary. To avoid giving more medication than required, a check on the Veratrum requirement from time to time therefore is as essential as is a check on the need for a weekly mercurial diuretic in a cardiac patient.

Although one cannot deny the efficacyindeed the sometimes life-saving qualities of hexamethonium and apresoline therapy in patients with severe hypertension—the potential hazards incumbent in the use of these agents cannot be emphasized too strongly. Hexamethoniuminduced collapse reactions, constipation and impotency in men, and apresoline-induced headache and palpitation are familiar to all who use these medications. Recently, however, notably through the studies of Perry and Schroeder, Dustan et al., as well as other investigators, even more serious toxic reactions have been reported to follow long-term administration of high doses of both these agents, e.g., interstitial pneumonia due to hexamethonium and a lupus erythematosus-like picture due to apresoline. 12-14

Since hexamethonium and apresoline are capable of producing such serious side effects, exceeding caution should be exercised in selecting patients for therapy; certainly no patient with normal eyegrounds or grade I hypertensive retinopathy should be subjected to this type of medication. The large majority if not all patients with grade II retinopathy can be adequately and safely controlled with the rauwiloid plus veriloid plus amytal combination. Consequently, more drastic therapy is indicated only in patients with grade III or grade IV retinopathy.

Once therapy with hexamethonium and/or apresoline has been instituted, frequent checks on the need for large dosages of either or both drugs are necessary. As is the case with our veriloid-treated cases, we found that the hexamethonium and apresoline doses could be reduced by one-third in four cases within seven months after institution of therapy. If more serious toxic reactions are to be prevented, minimum effective dosage must always be used.

Perry and Schroeder reported that Rauwolfia could not be substituted for apresoline. 13 The addition of rauwiloid to the regimen of our patients taking hexamethonium (parenterally or orally) and apresoline made possible a reduction in the hexamethonium dosage of one-third or more in all but five cases and omission of apresoline entirely in all but four cases. In nineteen of twenty-one patients the level of arterial pressure and status of congestive failure remained either unchanged or showed improvement with the addition of rauwiloid to optimal dosage of hexamethonium and apresoline. By substituting a non-toxic drug for a potentially toxic one, and by reducing the dosage of another, unpleasant side reactions were minimized or alleviated completely; the patients felt better, they continued to do well or improved, and the danger of long-term reactions was reduced or eliminated.

Preliminary observations with pentapyrrolidinium suggest that this drug is five times more potent than hexamethonium, is less toxic and absorbed more dependably. Because of these qualities it will probably replace hexamethonium in the hypotensive armamentarium. It is worth noting, therefore, that rauwiloid is capable of reducing the dosage requirement of pentapyrrolidinium significantly.

As stated at the outset, the objectives of this study were to provide the answers to several questions. Our data to date have provided the answer to some of these and have also given us a reasonable basis for predicting answers to the others.

- 1. Rauwiloid is of value in mild to moderate degrees of hypertension, and results obtained with the drug are superior to those obtained with mild sedation alone. In the more advanced cases rauwiloid should be supplemented with more potent hypotensive agents such as veriloid, hexamethonium, or other ganglionic blocking agents, and/or apresoline.
- 2. No appreciable benefit was seen in congestive failure and there was no valid evidence that the status of the hypertensive cardiovascular disease was changed appreciably by rauwiloid alone. However, on combination therapy congestive failure was found to clear in several patients, and there is reason to believe that simply lowering the blood pressure slows the progression of vascular disease and may in time actually allow regression of organic changes.
 - 3. The addition of rauwiloid to veriloid re-

duces the dosage requirements for veriloid and widens the margin between the therapeutic dose of veriloid and the dose producing side actions.

4. By adding rauwiloid to hexamethonium and/or apresoline therapy it is possible to reduce the dose of these potent agents significantly and often to eliminate apresoline entirely, thus greatly reducing the incidence of toxic side actions.

SUMMARY AND CONCLUSIONS

The present status of our studies on eightynine hypertensive patients, treated with Rauwolfia alone or in combination with other more potent hypotensive agents, permits the following conclusions:

1. When used alone, rauwiloid proved to be definitely superior to the use of mild barbiturate sedation for the reduction of blood pressure and for the relief of anxiety in patients with normal eyegrounds or with grade I hypertensive

retinopathy.

2. When added to veriloid, rauwiloid frequently made it possible to reduce the dose of veriloid by one-third or more, thus reducing significantly the incidence of nausea and vomiting, and also enhancing the hypotensive effect.

3. When added to hexamethonium and apresoline in severe hypertension, rauwiloid made possible a reduction in the hexamethonium dosage by one-third or more in all but five cases and eliminated the need for apresoline entirely in all but four cases. The blood pressure remained the same or improved. The hexamethonium- and apresoline-induced side effects were either greatly reduced or eliminated altogether.

REFERENCES

1. WILKINS, R. W. New drug therapies in arterial hypertension. Ann. Int. Med., 37: 1144, 1952.

- WILKINS, R. W. and JUDSON, W. E. The use of Rauwolfia serpentina in hypertensive patients. New England J. Med., 248: 48, 1953.
- FORD, R. V. and MOYER, J. H. Extract of Rauwolfia serpentina in hypertension. GP, 8: 51, 1953.
- WILKINS, R. W. Combination of drugs in the treatment of essential hypertension. Mississippi Doctor, 30: 359, 1953.
- FORD, R. V. and MOYER, J. H. Preliminary observations of rauwiloid-hexamethonium combined therapy in hypertension. Am. Heart J., 46: 754, 1953.

6. Webster, M. B. Drug therapy in hypertension. (In press.)

 STUTZMAN, J. W., MAISON, G. L. and KUSSEROW, G. W. Veriloid, a new hypotensive extract of Veratrum viride. Proc. Soc. Exper. Biol. & Med., 71: 725, 1949; Hypotensive activities of fractions from green hellebore. Federation Proc., 8: 355, 1950.

8. Maison, G. L., Gotz, E. and Stutzman, J. W. Bioassay methods for derivatives of Veratrum viride. Federation Proc., 9: 299, 1950; Arch. internat. pharmacodyn., 85: 357, 1951; J. Pharmacol. &

Exper. Therap., 103: 74, 1951.

 STEARNS, N. S. and Ellis, L. B. Acute effects of intravenous administration of a preparation of Veratrum viride in patients with severe forms of hypertensive disease. New England J. Med., 246: 397, 1952.

- WILKINS, R. W. Veratrum viride and essential hypertension. New England J. Med., 242: 535, 1950
- 11. Kauntz, R. and Trounge, J. The hypotensive action of veriloid. *Lancet*, 1: 549, 1951.
- MORROW, J. D., SCHROEDER, H. A. and PERRY, H. M., Jr. Studies on the control of hypertension by hyphex: II, toxic reactions and side effects. Circulation, 8: 829, 1953.
- Perry, H. M. and Schroeder, H. A. Syndrome simulating collagen disease caused by hydralazine (apresoline). J. A. M. A., 154: 670, 1954.
- DUSTAN, H. P., TAYLOR, R. D., CORCORAN, A. C. and PAGE, I. H. Rheumatic and febrile syndrome during prolonged hydralazine treatment. J. A. M. A., 154: 23, 1954.
- Freis, E. D. Recent developments in the treatment of hypertension. M. Clin. North America, pp. 363-374, 1954.
- FINNERTY, F. A., Jr. and Fuchs, G. J. The Veratrum treatment of toxemia of pregnancy; a controlled study. Am. J. Obst. & Gynec., 66: 830-841, 1953.

Esophageal Varices in Non-cirrhotic Patients*

Esophagoscopic Study

Lt. Col. Eddy D. Palmer, M.C. and Irving B. Brick, M.D. Washington, D. C.

y esophagoscopic standards it has been found that 63 per cent of patients with portal cirrhosis who come under medical surveillance have esophageal varices. 1 Similarly, one-third of a group of patients with visceral schistosomiasis have been found to have varices.² Primary and secondary obstruction of the extrahepatic portal venous system is the third major cause of these lesions. It is known that other hepatic and systemic diseases may be accompanied by varices³ but expected incidences are not known because esophagoscopic data are not available. Autopsy examination is believed to be unreliable for investigation of variceal incidence, and it has been observed that roentgenologic study demonstrates varices in only a fraction of patients found by esophagoscopy to be affected.1

It was the purpose of the present study to investigate esophagoscopically the incidence of esophageal varices in adult patients whose liver biopsy showed certain types of abnormality other than portal or biliary cirrhosis, and whose physical findings and course appeared to exclude the diagnosis of portal vein obstruction. Emphasis was placed on correlations with the history of hematemesis and the presence of other potential upper gastrointestinal bleeding lesions.

MATERIAL AND METHODS

Sixty-two hospitalized patients with various primary or secondary liver affections were studied. (Table 1.) Liver biopsies were taken with the Vim-Silverman needle. The Eder-Hufford esophagoscope, which is fitted with a telescope giving four-diameter magnification and which permits various manipulations under magnification, was used. The methods for measuring severity and extent of esophageal varices and the criteria for classifying severity, as used herein, have already been described.⁴

FINDINGS

Chronic Cardiac Failure. Six men and a woman, aged forty-two to seventy-five years, were studied. Six had arteriosclerotic hypertensive heart disease and one had tricuspid insufficiency associated with an obscure chronic collagen disease. All were under treatment for chronic congestive failure. Liver biopsy in all showed chronic passive congestion and, in addition, there was minimal portal fibrosis in one and moderate fatty metamorphosis in another.

Esophageal varices were found in four. (Table I.) They were classed as severe in one, moderate in one and mild in two. The distal two-thirds of the esophagus was involved in all. One patient was examined esophagoscopically on three occasions over a three-month period, during which hepatomegaly improved slightly. The varices meanwhile extended to involve all of the esophagus. Gastric varices were excluded by means of gastroscopy in three instances.

The findings in this group were unique in that in three instances the size of the varices was greater in the middle third of the esophagus than in the distal third, a situation not encountered during esophagoscopic study of 235 cases of portal cirrhosis. The fourth patient's varices were no larger in the distal third than they were in the middle third.

Portal venous pressure in one patient, measured transesophagoscopically, ³ was 460 mm. of water. The portal circulation time ⁵ in another was forty-two seconds.

Fatty Liver. Study of nine patients with hepatomegaly and severe fatty metamorphosis of the liver showed no esophageal varices. Six had a history of hematemesis or were studied during hemorrhage, and in four there were five demonstrable upper gastrointestinal lesions which might have been responsible. One patient was

* From the Gastrointestinal Sections, Walter Reed Army Hospital, and Georgetown University Hospital and School of Medicine, Washington, D. C.

treated by emergency gastric resection for bleeding duodenal ulcer.

Portal Fibrosis. Twenty-four patients had liver disease characterized by fibrosis of the portal areas but little perilobular extension. In addition, there was reactive hepatic cell

ease. There was improvement in the varices of three patients, slight worsening in one and no change in the other.

The portal venous pressure was measured in three patients and the readings were, respectively, 360, 240 and 120 mm. of water.

TABLE I

DATA REGARDING VARICES AND HEMORRHAGE AMONG SIXTY-TWO PATIENTS WITH NON-CIRRHOTIC LIVER

DISEASE

	Chronic Heart Failure	Fatty Liver	Acute Hepatitis	Sarcoid	Congenital Hemolytic Icterus	Amebic Hepatitis	Portal Fibrosis
No. patients	7	9	14	4	2	2	24
by esophagoscopy	4	0	8	0	1	1	8
by x-ray	1	0	0	0	0	0	0
Gastric varices:							
no. gastroscoped	3	5	14	2	2	2	9
no. found	0	0	0	0	0	0	0
Portal pressure:							
no. measured	1					1	3
average, mm. H ₂ O	460					285	240
History bleeding	2	6	0	1	0	0	9
Other lesions:							
gastric ulcer	2	1	0	0	0	0	2
duodenal ulcer	1	2	0	1	0	0	5
esophagus diverticulum	0	0	0	0	0	0	1
hiatus hernia	0	1	0	0	0	0	0
esophagitis	0	1	0	0	0	0	0

pleomorphism in one, round cell portal infiltrate in six and fatty metamorphosis in one. Three of the patients were women, and the ages ranged from nineteen to sixty-eight years. There was hepatomegaly in seventeen, splenomegaly in four and vascular spiders in one. Ten had a history of hepatitis, all confirmed by review of previous records, and eleven were chronic alcoholics.

Nine of the patients had a history of hematemesis. Seven had a total of eight possible bleeding sites other than varices.

Esophageal varices were found in eight. They were classed as moderate in five and mild in three. One-third of the organ was involved in four, one-half in one and two-thirds in three. The distal esophagus was most severely affected in all. No gastric varices were found during gastroscopic examination of nine patients.

Five of the patients with varices were examined esophagoscopically more than once over periods of from nine days to one month, while under hospital treatment for chronic liver disActive Phase of Acute Infectious Hepatitis. Fourteen males, aged nineteen to forty-three years, were examined. The possibility of homologous serum hepatitis existed in two. The examinations were made from seven days to five weeks after the onset of illness. Liver biopsies were typical in all. In addition, those from two patients showed fatty metamorphosis. None contained fibrosis. None of the patients had a history of recognized bleeding from the gastrointestinal tract.

Although gastric varices could be found by gastroscopic examination in none, esophageal varices were present in eight. They were classed as mild in seven and moderate in one. The entire esophagus was involved in one, distal two-thirds in three, distal one-half in one and distal one-third in three. In all patients the varices were largest close to the esophagogastric junction.

Esophagoscopic examination was repeated in two patients, eleven and twelve weeks after the first, when complete laboratory and clinical recovery had been attained. There was no change in the appearance of the varices in one, and in the other there was moderate improvement.

AMERICAN JOURNAL OF MEDICINE

Sarcoidosis. Four patients whose liver biopsy was positive for sarcoidosis but no other disease were examined. No varices were found. Two studied gastroscopically showed no gastric varices. One patient who had had a severe hemorrhage was found to have gastritis, and emergency gastric surgery revealed sarcoidosis of the stomach.

Congenital Hemolytic Icterus. Two patients with the non-spherocytic form of this disease were studied because an unrelated circumstance had led to the esophagoscopic detection of varices in one. Three examinations of this patient over the course of five months showed stable mild varices involving the distal one-third of the organ. The other patient's esophagus was normal. Liver biopsy in both cases showed great amounts of pigment, without other alteration.

Amebic Hepatitis. Two young men with the clinical diagnosis of amebic hepatitis were examined before therapy was instituted. Liver biopsy showed hepatic cell pleomorphism, tiny areas of focal necrosis and minor portal infiltration. Gastroscopic examination of both and esophagoscopic examination of one were normal. Three esophagoscopies over a seven-day interval in the other revealed stable mild varices of the distal three-quarters of the esophagus. The portal venous pressure was found to be 285 mm. of water.

COMMENT

Routine use of the esophagoscopic method for detection of varices promises to help elucidate the natural history of varices and of portal hypertension because it permits recognition of small and presumably early lesions. It can supply information to fill the important hiatus between inception and development of the very large, roentgenologically detectable lesion. In the present series only one of twenty-two cases of esophageal varices was detected by x-ray study. It has already been demonstrated that "small" varices may be important clinically.³

There is suggestive evidence here that the native portacaval shunts across the gastro-esophageal junction are more readily available for portal use than has been suspected. Anatomic study of dead tissue has shown these connections normally to be present but by postmortem technics the vessels appear to be very small, as if they require prolonged venous demand before they can become varices. In the present study varices were encountered as soon as seven days

after the onset of acute hepatitis. Quite clearly, important information regarding the natural history of esophageal varices will accrue from esophagoscopic study of a large series of patients with acute hepatitic processes.

Hemorrhage from esophageal varices must be considered a rare complication of chronic heart failure. The studies of Castberg⁶ and others have shown that chronic passive congestion of the liver predisposes to deposition of connective tissue and at times to development of true cirrhosis. In addition, fibrous vascular disease, limited largely to members of the hepatic vein system, constitutes a prominent pathologic feature. Autopsy studies have frequently shown varices in patients dying of chronic congestive failure. In one series of thirty-one instances of varices detected at autopsy, in seven there had been heart failure without other liver disease.7 In another autopsy study chronic heart disease was found to be the cause in five of 257 cases of varices.8 The series of Weinberg9 showed an unexplained preponderance of heart disease as the major autopsy diagnosis associated with varices.

There are practical reasons for omitting esophagoscopic examination during congestive failure, and the present series is very small. Nevertheless, the discovery of varices in four of seven patients is of considerable importance. The two who hemorrhaged massively constituted difficult treatment problems. One was found to have both a gastric and a duodenal ulcer in addition to the varices. In the other the bleeding was considered to have been of variceal origin, although it had stopped a few days before esophagoscopy could be performed.

There is no ready explanation for the tendency toward maximum variceal involvement of the mid-esophagus in congestive failure. The tendency has not been noted in some autopsy studies^{7,9} but it is questionable whether measurements of varix diameter at different levels after death is a valid means of judging the severity of the lesions as they existed during life. The mechanisms of portal hypertension in heart failure have been well discussed by Rack and colleagues.⁷

The case of hemolytic anemia and varices is difficult to understand in view of the liver biopsy findings. Hyman and Southworth¹⁰ have described eight hemolytic anemia patients with histologically proven liver disease—including

four with cirrhosis—but biopsies in the present patients showed only hemosiderosis.

In order to understand inclusion of patients with hepatic sarcoidosis in the present series, one must refer to the paper of Mino and colleagues. 11 They described a singularly important case of liver disease due to sarcoidosis and, although no mention was made of varices and although portal hypertension was not proved, histologic examination of liver specimens showed a mechanism whereby sarcoidosis may cause serious interference with intrahepatic portal flow. There was striking mural infiltration of several of the larger, apparently sublobular, veins by sarcoid granulomas. The result was encroachment upon the vein lumina. No varices were found in the four patients reported in the present series. Their liver biopsies had shown no apparent vein compression or direct involvement by granulomas.

SUMMARY AND CONCLUSIONS

1. Sixty-two patients with various histologically proven liver diseases other than cirrhosis and without clinical suspicion of portal vein disease were studied esophagoscopically. Varices were found in four of seven patients with chronic heart failure, eight of fourteen with active virus hepatitis, one of two with hemolytic icterus, one of two with amebic hepatitis and in eight of twenty-four with simple portal fibrosis. Varices were not found in nine instances of fatty liver and in four of hepatic sarcoidosis.

2. It is concluded from the observed incidence of varices in these non-cirrhotic diseases that the native portacaval anastomoses across the gastroesophageal junction may quickly respond

to an increase in portal pressure by developing into significant varices; that during the course of certain liver diseases, believed to be pre-cirrhotic, varices may already have developed; and that the presence of such varices is not necessarily the explanation for observed hemorrhage.

REFERENCES

- BRICK, I. B. and PALMER, E. D. Incidence and diagnosis of esophageal varices in cirrhosis of the liver: an esophagoscopic study. *Gastroenterology*, 25: 378–384, 1953.
- 2. Palmer, E. D. and Jahnke, E. J., Jr. Observations on portal hypertension secondary to schistosomiasis. Am. J. Trop. Med. & Hyg., 3: 139-146, 1954.
- PALMER, E. D. The Esophagus and Its Diseases, p. 554. New York, 1952. Paul B. Hoeber.
- PALMER, E. D. On correlations between the level of the portal venous pressure and the size and extent of esophageal varices in portal cirrhosis. *Ann. Surg.*, 138: 741–744, 1953.
- GIGES, B. and TESCHAN, P. E. The portal circulation time in cirrhosis of the liver following portacaval anastomosis. J. Lab. & Clin. Med., 40: 537-540, 1952.
- CASTBERG, T. Vascular changes in chronic passive congestion of the liver. Acta path. et microbiol. Scandinav., 30: 358-370, 1952.
- RACK, F. J., MINCKS, J. R. and SIMEONE, F. A. Observations on etiology of esophageal varices. *Arch. Surg.*, 65: 422–429, 1952.
- GARRETT, N., JR. and GALL, E. A. Esophageal varices without hepatic cirrhosis. Arch. Path., 55: 196-202, 1953.
- Weinberg, T. Observations on the occurrence of varices of the esophagus in routine autopsy material. Am. J. Clin. Path., 19: 554-557, 1949.
- HYMAN, G. A. and SOUTHWORTH, H. Hemolytic anemia associated with liver disease. Am. J. M. Sc., 221: 448-456, 1951.
- MINO, R. A., MURPHY, A. I., JR. and LIVINGSTONE, R. G. Sarcoidosis producing portal hypertension: treatment by splenectomy and splenorenal shunt. Ann. Surg., 130: 951-957, 1949.

Effect of the Oscillating Bed and Tilt Table on Calcium, Phosphorus and Nitrogen Metabolism in Paraplegia*

DEREK M. WYSE, M.D., C.M., F.R.C.P. (C) and C. J. PATTEE, M.D.

Kitchener, Ontario Montreal, Quebec

ALTHOUGH great strides have been made in recent years in the therapy of paraplegia, several problems still remain. Outstanding among these are the development of disuse osteoporosis and the presence of large amounts of calcium in the urine, the latter condition often contributing to the formation of urinary calculi. Since these metabolic disturbances play a significant part in the morbidity and sometimes in the mortality rates of paraplegic patients, any practical procedure which would alter these metabolic disturbances for the better would be an important step in the therapy of these patients.

The metabolic changes in paraplegic patients have been investigated in great detail in recent years, and much has been learned by investigation into the alterations in metabolism of normal immobilized subjects as well as those which follow various forms of trauma. We shall review very briefly the highlights of these investigations; for a detailed review of the subject the reader is referred to the articles previously published by the authors.1 As regards protein metabolism, the paraplegic patient does not differ significantly from any individual who has undergone a severe operation or has had an accident, in that he shows the "catabolic response," a marked urinary loss of nitrogen independent of nitrogen intake for a variable period after the stress. Cooper et al.² report that the nitrogen loss lasts longer than in other forms of trauma, as long as six months. In addition, many patients are reported to have hypoproteinemia. This greater protein loss might be due to the presence of decubitus ulcers and to mental depression associated with poor appetite. Similar qualitative but less marked quantitative changes have been

shown by Deitrick et al.³ following the immobilization of normal individuals.

Howard et al.⁴ have demonstrated a marked increase in urinary calcium in patients with fractures of the femur and following osteotomy. Deitrick et al. showed similar but lesser changes with immobilization alone. In Howard's cases there was a steady rise in calcium excretion, reaching a plateau in one month and returning to normal only upon ambulation. Freeman⁵ found that paraplegic patients showed a very similar phenomenon and he emphasized the point that the hypercalcinuria recedes only upon ambulation.

Somewhat similar changes have been observed in regard to phosphorus metabolism but these are less marked and less constant than the protein and calcium alterations.

The negative calcium balance results frequently in disuse osteoporosis affecting the lower extremities. The incidence of this condition in paraplegia has been reported variously from 30 to 60 per cent; in some patients the osteoporosis appears to contribute to fractures since these often occur with minimal trauma.

While modern urologic procedures such as tidal drainage have reduced the frequency of urinary calculi to a considerable degree, recent figures, quoted in previous articles, show that the problem is still a serious one especially when the calculi form above the bladder.

The endocrine glands have been investigated by several observers, who have found gynecomastia, testicular atrophy, low 17-ketosteroid excretion and low basal metabolic rates.

It is well known that the vasomotor system of paraplegic individuals is unstable, especially in the paralyzed extremities, and this instability

^{*} From the Clinical Investigation Unit, Queen Mary Veterans Hospital, Montreal, Quebec.

often causes difficulties at the time of ambulation, syncope frequently occurring and petechiae of the feet often causing concern to both physician and patient.

AIM OF STUDY

Since ambulation appears to be the key to restoration to normal of many metabolic and physiologic abnormalities following immobilization, the aim of the study was to attempt certain procedures which would imitate ambulation while the patient was still bedridden. It was hoped that in this manner the disuse osteoporosis and resultant hypercalcinuria, with its consequent role in the formation of urinary calculi in paraplegic patients, could be prevented or at least ameliorated.

The rationale of this procedure was that ambulation creates certain ill defined stresses and strains on the immobilized bones which would otherwise be lacking; it was postulated that one or more of three mechanisms might be involved: (1) weight-bearing through the long bones of the lower extremities; (2) pulls and stresses on muscular attachments to bone by muscle contractions; (3) circulatory changes in the lower extremities. Any one or combinations of these factors might play a role in stimulating normal osteoblastic activity. Since muscle pull is absent in flaccid paralysis, attention was focussed on the other two mechanisms.

PROCEDURES

The Sanders Oscillating Bed. The first method of imitating ambulation was by means of the oscillating bed which has been shown by Whedon et al. 14 to modify the metabolic changes of immobilization per se, as well as some of the physiologic alterations. Although these workers thought that weight-bearing played a major part in this effect, we believed that little more than 20 per cent of the body weight would be borne through the lower extremities, and then only at the lowest point of the oscillation. It would appear more likely that circulatory changes constitute the important factor in the effect of the bed.

The oscillating bed was used in four of the five cases studied, the bed being in motion for eight hours a day. It was set so as to travel from the horizontal position to 21 degrees below the horizontal plane with the foot of the bed down, a complete cycle taking one minute and twenty seconds. All patients adapted themselves very

rapidly to the motion of the bed, and most rather enjoyed its motion.

The Tilt Table. If weight-bearing through the lower extremities rather than changes in circulation is the main factor in producing stresses and strains on bone, a more direct method of producing such weight-bearing than that allowed by the oscillating bed seemed more desirable. The most simple, safe and practical method of producing such weight-bearing appeared to us to be the use of a tilt table, although several other means are possible, e.g., application of traction to the lower extremities or the attachment of wooden supports to a Stryker frame and then tilting it, 6 or the recently reported method by Covalt et al.7 of placing the patient on a board, strapping him to it and then standing the board up at the edge of the bed. While simple tilt tables may be readily devised, we had at our disposal an old fluoroscopy table which could be cranked manually and which was kept on the ward. The technic of getting the paraplegic patient into the upright posture on the tilt table is not difficult, and after the first time requires only the aid of a trained orderly since the patient is able to help considerably. Before the patient is placed on the table, posterior splints padded with felt are applied to his lower limbs, being held in place by crepe bandages into which is incorporated an elastic strap to support the foot. By this technic the knees are prevented from flexing while the feet are held at right angles to the legs. The patient is then placed on the table with the feet against the foot-board, an abdominal binder is secured about the upper abdomen, a crepe bandage is placed around the knees and the table is then cranked into the upright posture. A bar is available for the patient to grasp for support, although this is usually not necessary, as will be seen in Figure 1. This method produces the bearing of 95 per cent of the patient's weight through the lower extremities if he does not hold onto the bar, and 90 per cent if he leans on the bar.

All five of our patients were placed on the tilt table, all starting with five minutes in the upright position twice a day and gradually building up the length of time on the table, the maximum being in the fifth patient who was up as long as one hour and fifty minutes per day. The period on the tilt table was always divided into two parts, once in the morning, and once after lunch. Blood pressure and pulse were taken

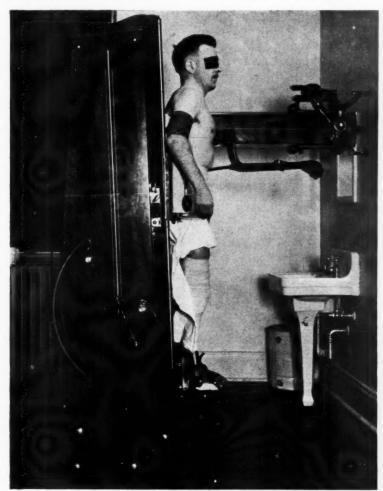


Fig. 1. The tilt table in upright position.

every five minutes in the first two weeks on the table.

All patients tolerated the upright posture well, although there was a tendency to dizziness if fever and malaise due to urinary "flare-ups" were present. It was believed that the period of time spent on the oscillating bed prior to being placed on the tilt table lessened the tendency to syncope. No outright syncope occurred in any patient. All patients showed small petechiae of the feet and ankles in the first week on the table but these rapidly disappeared. Color of the legs appeared to improve after the study had been carried on for a week.

PROTOCOL

Length of Study. The planned length of study was forty-eight days, divided into three periods. First, there was a control period of twelve days in which the patient was in bed receiving physiotherapy in most cases, consisting of passive movements of the lower extremities and

active movements of the arms. In addition, throughout the study routine ward procedures, such as turning the patient every two hours night and day, irrigation of the bladder with Solution G (citric acid-sodium citrate solution) twice daily and changing the indwelling catheter once a week, were carried out. After the control period a twelve-day period on the oscillating bed followed, and finally a period of twenty-four days on the tilt table.

However, only two of the five patients followed this plan of study. The first patient (M. L.), a "pilot" case, had a control period of twenty days in which the effects of altering the diet, physiotherapy, moving in a wheelchair and plastic repair of decubitus ulcers were carried out. Twenty days were spent on the oscillating bed and twenty-five days on the tilt table. The third patient (A. S.), whose paraplegia had been present for only one week, was placed on the tilt table immediately, the oscillating bed not being used; he was on the table for twenty-

six days and was followed up for twelve days after this, on bedrest alone. The fourth patient (K. B.) had his study interrupted for nine days at the completion of the oscillating bed period due to the occurrence of a febrile episode resulting from pyelonephritis. Otherwise his study

was carried out according to plan.

Diet. Prior to starting the study the patients were interviewed by the dietitian and a diet was outlined, the carbohydrate and fat being as close to the patients' previous eating habits as possible. An attempt was made to use a rotating diet but this was not often possible due to the heavy strain on laboratory facilities. The calcium and nitrogen intakes were analyzed: the phosphorus intake was calculated only. When the analyzed results were received from the laboratory, the difference between calculated and analyzed levels was met either by subtracting the excess calcium or by adding the needed calcium in the form of calcium chloride. This added calcium ranged from 0 to 300 mg. per day. The phosphorus levels were kept constant by the addition of monobasic sodium phosphate. The first patient, our "pilot" case, was on a calculated diet only. The daily calcium intake was around 1,100 to 1,200 mg., with slight variations between patients and in some there were swings due to refusal of food. Phosphorus intakes varied, the majority being fixed at 2,275 mg./day. Some were as low as 1,270 to 1,490 mg./day. An attempt was made in all patients except the first to maintain a high protein intake so that sufficient "nitrogenous building blocks" would be available when and if the osteoblasts were stimulated. This attempt was fairly successful, all patients but the first being maintained for most of the time at a level above 20 gm. of nitrogen per day. Fat intakes averaged 137 gm./day, and carbohydrate intake varied from 340 to 178 gm./day. Individual intakes are listed in the section on results. It was attempted to keep fluid intakes high, up to 4,000 cc. per day.

An aliquot of each diet was sent to the laboratory for analysis of calcium and nitrogen content and adjusted as described. The patients were required to eat everything on the trays; but if there were returns, these were sent to the laboratory for analysis.

Biochemical Determinations. The urine was collected via an indwelling catheter into a bottle kept on ice. Three-day pools were analyzed for calcium by the method of Clark and

Collip,⁸ phosphorus by the method of Gomori,⁹ nitrogen by the micro-Kjeldahl method, and creatinine. Stool was obtained once each morning by rectal touch, sometimes aided by the oral administration of licorice powder or liquid paraffin and rarely by the intramuscular injection of 1-2 cc. of prostigmine. Stool was pooled every three days at first but shortly thereafter six-day pools were collected. Calcium determinations of the stool were carried out according to the method of Corley and Denis. 10 A marker of 0.6 gm. carmine alum lake was given by mouth at 6 P.M. of the last day of each period, the first red stool being added to that period. In each period one or more determinations of serum calcium, phosphorus, alkaline phosphatase, urea nitrogen, albumin and globulin were performed. One determination of the 17-ketosteroid level according to the method of Callow et al.11 was carried out on a three-day pooled urine in each period in some of the subjects. Basal metabolic rates, urine cultures, Mosenthal tests, phenolsulfonphthalein and urea clearance tests were performed at the end of each period in three subjects. Routine urinalysis was carried out every three days in all patients.

Several sources of error in collection and estimation were obvious. One of the major difficulties was the proper collection of stool; this was often an impossibility due to involuntary movements. Loss of nitrogen via weeping decubitus ulcers was anticipated but none of the patients studied in regard to nitrogen metabolism had decubitus ulcers, with the exception of two patients, (M. L.) whose trochanteric ulcers were covered with skin flaps during the study and (K. B.) who had a small superficial sacral ulcer which exuded very little serum. A rather serious difficulty that presented itself was the state of the calcium in the urine. A certain percentage is present in the sediment so that if one does not shake the specimen prior to pipetting off the aliquot, some calcium will be lost, while if it is shaken an uneven distribution of particles may occur. This difficulty might be overcome by acidifying or by adding hyaluronidase to the urine but then calculi would be dissolved as well as the sediment, resulting in sudden high peaks. We were unable to find a length of time at which the sediment was dissolved while the stones were not. After experimenting with acidified and non-acidified urine, we concluded that the best technic which would give the most consistent, if not the highest

results, was to shake non-acidified urine in a constant manner for one minute, then let the specimen settle for five minutes, giving the larger particles opportunity to settle down, and then pipetting the aliquot. Another source of error could be the presence of calcium phosphate encrustations on the catheter tip. We found that these do not constitute a significant source of error since encrustations representing one week contained only 5–10 mg. of calcium, the majority of the encrustations consisting of organic matter.

X-rays. X-rays of the long bones of the lower extremities were taken at the beginning and end of study, using an aluminum densitometer for comparison. While it was realized that this gave only a crude indication of changes in bone density, it appeared to be the only practical method of corroborating the calcium balance studies since radioactive strontium and calcium are not applicable to human study. The possibility of using the intravenous calcium test described by Schilling and Lazlo¹² was considered but in view of the already elevated urinary calcium excretion in paraplegics the test seemed impractical. Flat plates of the kidneys, ureters and bladder were also taken at onset and finish of studies to search for changes in calculi present or the appearance of new

Subjects. Eight patients were studied of whom three were discontinued shortly after the start of studies as they were unsuitable. Of these three, one was a fifty-seven year old male in whom "hysterical" paraplegia had developed, in that he had voluntarily remained in bed for twelve years following low back pain from osteoarthritis of the spine and the prolonged bedrest had brought about marked disuse atrophy of the lower extremities; his study was discontinued because he was excreting very low amounts of calcium in the urine, of the order of 50 mg. per twenty-four hours. The second discontinued case was a twenty-six year old traumatic paraplegic patient who was unable to cooperate in regard to diet, while the third was a fifty year old man who was immobilized in a body spica for osteoarthritis of the hips. He was also discontinued due to inability to cooperate. Of the remaining five patients all had paraplegia resulting from trauma in three, transverse myelitis in one and extradural metastasis of bronchial carcinoma in another. All were males, with ages ranging from twenty-six to forty-one years. The level of the lesion in the three traumatic cases was D11-12, the others being at D6-7 and D8, respectively. The duration of the paraplegia prior to beginning the study varied from one week to thirteen months. Case histories of the patients studied are as follows.

CASE REPORTS

Case I. M. L., a thirty-five year old man, fell from a tree and sustained a fracture-dislocation at D11-12, with complete flaccid paraplegia and loss of bladder and bowel functions thirteen months before study. He also sustained a skull fracture and was unconscious for one week following injury. Laminectomy, reduction and decompression of the spinal fracture were performed on the day of injury. Spinal fusion was carried out but due to poor cooperation on the part of the patient the bone fragments became angulated and subsequently large trochanteric decubiti developed, which became infected. The bladder was emptied by manual compression. On admission an indwelling catheter was inserted and during the course of study plastic surgery was performed on the ulcers after infection had been combatted. The patient had been sitting in a chair at home prior to admission but this was discontinued due to the presence of the decubitus ulcers. Nutrition had been poor and plasma proteins were low.

Case II. H. J., a thirty-two year old man, sustained a fracture-dislocation at D11-12 following trauma caused by a telephone pole falling on his back four months prior to study. Complete flaccid paralysis below the lesion occurred following the trauma. He was treated by application of a plaster cast. A retention catheter was inserted and the patient was still dependent upon this form of drainage at time of study. A slight amount of spasm of the lower extremities was present and a small deep sacral ulcer and one superficial ulcer over the right anterior iliac spine were noted, but these were almost completely healed at time of study.

Case III. A. S., a forty-one year old man, developed chest pain mainly on the left side posteriorly, and a cough productive of yellowish mucoid sputum without fever for nine days prior to admission. Physical examination of the chest revealed increased breath sounds over the left upper chest anteriorly. Chest x-rays and tomograms revealed an area of increased density, homogeneous in appearance, occupying

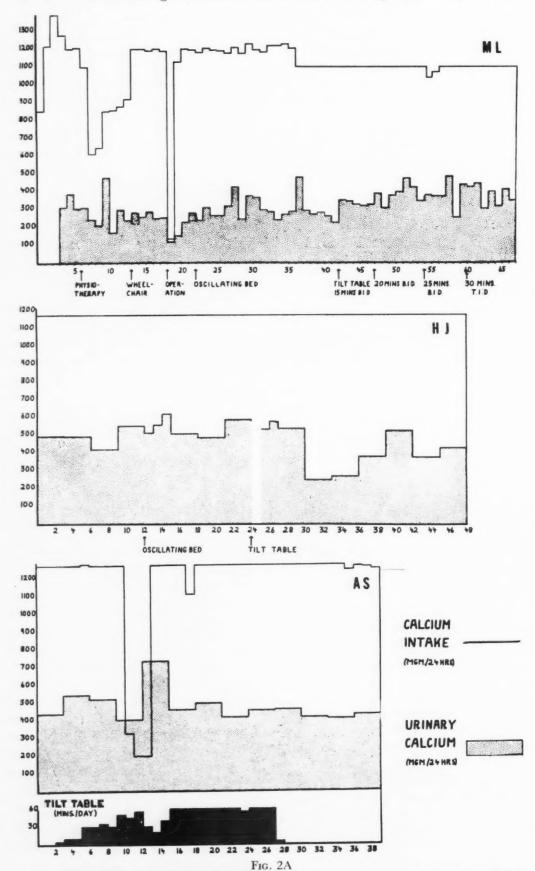


Fig. 2A. Urinary calcium excretion in three paraplegic patients, showing the effect of oscillating bed and tilt table.

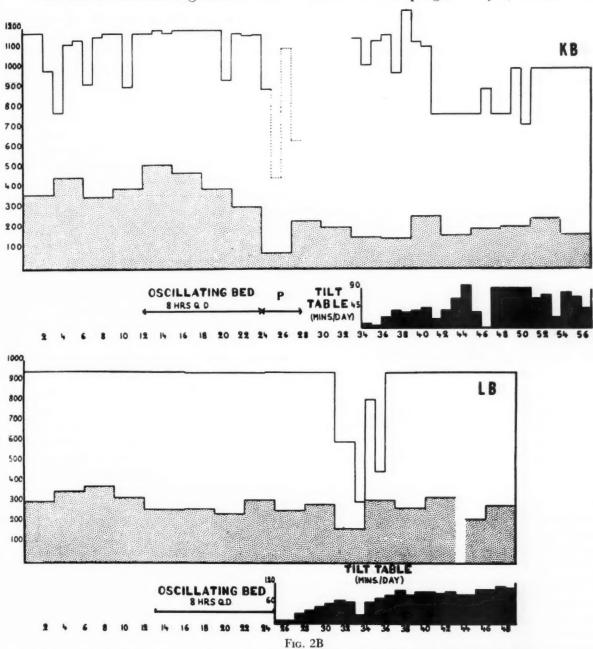


Fig. 2B. Urinary calcium excretion in two additional paraplegic patients, showing the effect of oscillating bed and tilt table.

the left upper lung field and a smaller mass near the left hilus. Bronchoscopic examination was unsuccessful. A lung needle biopsy from the affected area revealed undifferentiated neoplastic cells. The patient, who was schizophrenic, refused operation. Three weeks after admission, over a three-day period, a complete flaccid paraplegia gradually developed below D8; examination of the cerebrospinal fluid was noncontributory and x-rays of the spine did not reveal any evidence of an osteolytic lesion. The patient was studied beginning one week after

the onset of the paraplegia. During the study he lost weight, his appetite decreased and his condition gradually deteriorated. He died ten weeks after the onset of the paraplegia and autopsy confirmed the clinical diagnosis, an epidermoid type of bronchial carcinoma of the left upper lobe being found, with an extradural metastasis at D8.

Case IV. K. B., a thirty year old man, developed gradual weakness and numbness first of the right leg, then of the left, accompanied by backache. At the end of one week both legs

652

were paralyzed and the numbness had extended to the epigastrium. Physical examination revealed angiomatosis of the left fundus, flaccid paresis and absent reflexes of the lower extremities with absence of sensation below D6-7. Bladder and rectal sphincter controls were lost. Laminectomy was performed, revealing a uniform swelling of the cord at this level in keeping with a transverse myelitis. Serologic and spinal fluid examinations for syphilis were negative, and no other specific infection could be discovered. The early cerebrospinal fluid findings, together with the clinical picture, were suggestive of an acute necrotic myelopathy. There was no recovery of function at any time. The patient was studied two months after onset of

Case v. L. B., a twenty-six year old man, was injured in a mine accident, which caused a fracture-dislocation at D11 and D12 with flaccid paraplegia and loss of sensation below that level. Open reduction of the fracture with internal fixation was carried out shortly after the injury. The patient was studied one month after the accident. During the study there was development of some moderate spasticity of the lower extremities, and there was also some return of voluntary motor power in the left leg.

RESULTS

- A. Effect on Calcium Metabolism. The effects of paraplegia in calcium metabolism and the attempts to modify them by the use of the oscillating bed and tilt table will be seen in Figures 2 to 4.
- 1. Urinary calcium: (a) Initial levels: All control values were well above normal, the average being 300, 500, 500, 400 and 300 mg. per twenty-four hours, respectively, in the five subjects. The first patient, M. L., during his control study was given physiotherapy and allowed to sit in a wheelchair; he was given a variable diet to ascertain his average intake. There was no constant parallel between the calcium intake and urinary excretion of calcium. However, on the day of operation, when the calcium intake was limited to 131 mg., the output for that day was the lowest during the study, 115 mg. Daily urine collections rather than three-day pools were estimated in this patient.
- (b) Levels on oscillating bed: In patients M. L., H. J. and L. B. no change in urinary levels were noted during the period on the oscil-

- lating bed. In one patient (K. B.), however, there was a steady gradual decrease in excretion while on the bed, from 515 mg. per twenty-four hours to 307 mg. per twenty-four hours. The day after the oscillating bed period had ended pyrexia suddenly developed in this patient and there was evidence of pyelonephritis which was treated with penicillin and streptomycin. During the acute febrile period the urinary calcium fell to only 77 mg. per twenty-four hours; the calculated intake for this period was also lower than his usual analyzed intake and he was removed from his diet for the nine days following onset of the pyrexia, during which time the urine calcium continued its gradual progression downward noted in the oscillating bed period. One patient (A. S.) was not placed on the oscillating bed.
- (c) Levels on the tilt table: There was a variable response to the tilt table. One patient (M. L.) showed a slight rise in urinary calcium excretion, two (A. S. and L. B.) showed no significant change while another (H. J.) showed a sudden drop to almost normal levels after one week on the table, i.e., just when he had reached his maximum time on the table. This drop was maintained for six days, then gradually rose to higher values but not quite as high as control levels. As already mentioned, A. S. was placed on the tilt table at the onset of studies. This was done to study the effect of the table on paraplegia in its earliest stages; it will be recalled that the patient had been paraplegic for only one week. Even at this early date the urinary calcium had risen to very high levels (400-500 mg. per twenty-four hours), and on one threeday period rose to a peak of 735 mg. per twentyfour hours. The tilt table did not appear to alter this hypercalcinuria since the urinary levels remained constant for ten days after the tilt table had been discontinued.
- 2. Stool calcium: The difficulties of accurate estimation of calcium in feces are well known. An additional difficulty was encountered in paraplegic patients due to the frequency of involuntary bowel movements. Three-day pools were collected in the earlier part of the study but later six-day pools were instituted in an attempt to avoid the wide swings. In general, calcium excretion in the stool followed the intake, as is well shown in Figure 3. No definite effects on the oscillating bed or tilt table were noted. To conserve space, only one chart is shown.

3. Calcium balance (a) Initial levels: Strangely, three patients (M. L., K. B. and A. S.) were in positive balance in the control period, M. L. showing a retention of up to 500 mg./day. It will be recalled that this patient was the only

period of positive balance also in the control period. L. B. also showed a brief period of positive calcium balance on the tilt table but this was related to a period of reduced intake and more markedly reduced fecal excretion.

LBd-26YRS-PARAPLEGIA DII-12-I MONTH DURATION

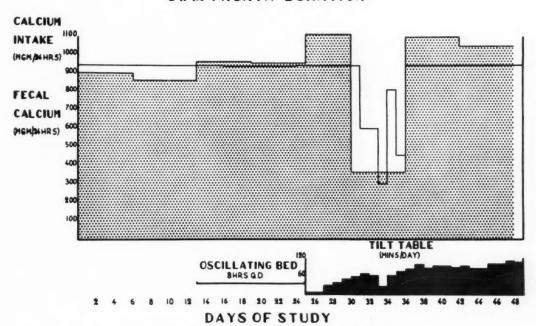


Fig. 3. Fecal calcium excretion in a typical patient.

one in this study whose lesion had been present for a considerable length of time (thirteen months). K. B. also showed a positive balance initially but this rapidly fell to equilibrium and to negative balance; it was believed that the initially high balance was due to poor stool collection at that time. The same fault probably accounts for the initially marked positive balance in A. S. H. J. showed a considerable swing in balance during the control study, being in positive balance in the middle of the period and in negative balance for the remainder; this corresponded to swings in stool levels. L. B. was in steady negative balance, of the order of -300 mg./day, throughout the control period.

(b) Balance on oscillating bed: No effect on calcium balance was noted in three of the four patients. In one (K. B.), however, there was a period of positive balance for most of the time on the oscillating bed and this was partly related to decreased urinary excretion.

(c) Balance on tilt table: In H. J.'s study there was a six-day period of positive balance related to lowered urinary excretion of calcium on the tilt table; however, the patient had shown a

The other three patients showed no definite trend. (Fig. 4.)

B. Effect on Phosphorus Metabolism (Fig. 5). The effects of the tilt table on the urinary phosphorus level are noted in Figure 5. (The chart of only one patient, A. S., is shown.) Of the four patients studied, all were kept on a calculated intake of 2,275 mg. phosphorus per day with a minor variation only, except in K. B. who showed several lower values due to returned food. Neither the oscillating bed nor the tilt table showed any decided effect on urinary phosphorus excretion, except for one patient (A. S.) in whom the tilt table period was accompanied by a significant gradual fall in urine phosphorus (from 1,620 to 1,100) on a constant intake. This appeared to be all the more significant since the urinary phosphorus rose after a discontinuation of the tilt table. In the other patients, however, no such correlation could be found.

C. Effect on Nitrogen Balance (Fig. 6). The nitrogen intakes and urinary nitrogen excretions on the four patients studied are charted in Fig. 6. All patients were maintained on a high



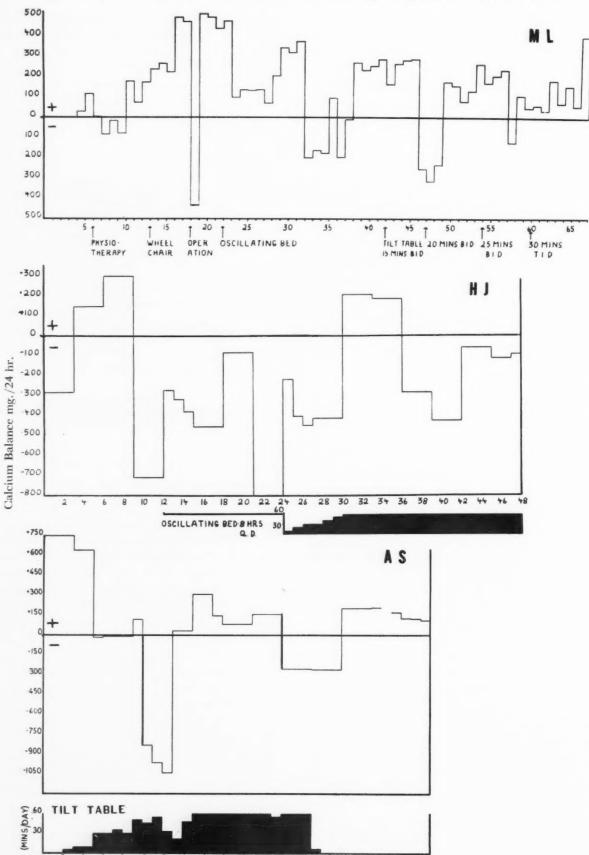


Fig. 4A. Calcium balances in three paraplegic patients, showing effect of oscillating bed and tilt table.

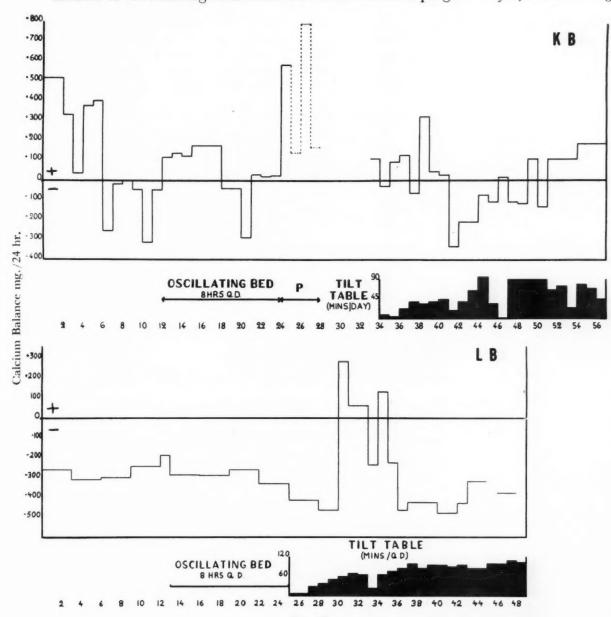


Fig. 4B. Calcium balances in two additional paraplegic patients, showing effect of oscillating bed and tilt table.

nitrogen intake well above 20 gm. per day in most instances. K. B. and L. B. were in nitrogen equilibrium for the greater part of the time, even though their injuries were only of two and one months' duration, respectively. H. J., whose injury had occurred four months previously, was in positive balance while A. S., with paraplegia of one week's duration, was in marked negative nitrogen balance. The urinary outputs regularly followed the level of intake, as is well demonstrated in A. S. The oscillating bed and tilt table did not affect the urinary excretion of nitrogen to any significant degree.

D. Effect on Plasma Proteins. Numerous plasma protein levels were estimated during

each phase of study. The first patient, M. L., with paraplegia of thirteen months' duration and a history of poor nutrition and bedsores, was the only one to have a low total plasma protein with depressed albumin and elevated globulin. This hypoproteinemia was not affected by the oscillating bed or tilt table. A. S., the patient with carcinoma who showed a negative nitrogen balance, also demonstrated a gradual fall in plasma albumin levels. The other patients failed to show any abnormalities or change on the oscillating bed or tilt table.

E. Effect on Serum Calcium, Phosphorus and Alkaline Phosphatase. All patients had a normal serum calcium, initially and throughout the

study. Initial serum phosphorus levels were within the normal range with a tendency in all subjects for higher levels, some slightly above the normal upper limit by the end of the study. The alkaline phosphatase was normal throughout in variation in 17-ketosteroid levels. All patients at one time or another showed low values (5.2, 3.7, 10.0 mg. per twenty-four hours). None of the patients showed signs of gynecomastia or testicular atrophy.

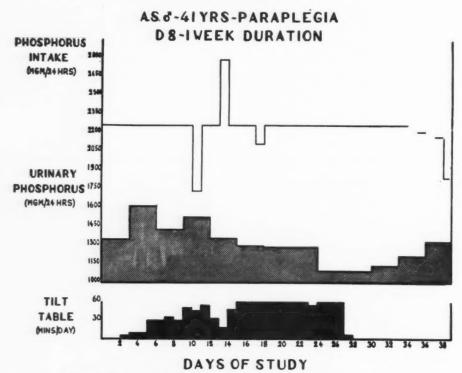


Fig. 5. Urinary phosphorus excretion in a paraplegic patient.

three of four patients studied; in the fourth (A. S.), who was dying from metastatic carcinoma, the alkaline phosphatase rose rapidly from normal levels initially to values up to 12.5 units.

F. Effect on Renal Function Tests. The results of phenolsulfonphthalein, urea clearance, Mosenthal and blood urea nitrogen tests were not remarkable. Only three of the five patients were studied in regard to renal function and all of these showed normal phenolsulfonphthalein and urea clearance tests, while two showed slight impairment of renal concentrating power as determined by the Mosenthal test. The blood urea nitrogen was normal in all four patients studied at all times.

G. Effect on Basal Metabolic Rate. The three patients studied were within the normal range of basal metabolic rate, except for -13 per cent on tilt table (H. J.) and -16.5 per cent on the oscillating bed (K. B.). These variations did not appear to be significant.

H. Effect on Urinary 17-Ketosteroids. In all three patients followed there was considerable

I. Effect on Urine Culture. All the subjects showed constantly heavy growths of various organisms in their urines, consisting of Bacillus proteus and Aerobacter aerogenes in all cases. In addition, moderate or light growths of Staphylococcus pyogenes, Bacillus coli, Bacillus paracolon and enterococcus were encountered. In K. B., during his acute febrile episode, a light growth of B. coli, indifferent streptococci and A. aerogenes was found. Most organisms were relatively insensitive to aureomycin, terramycin and streptomycin in vitro.

J. Effect on Radiologic Picture. 1. Osteoporosis: M. L. had definite radiographic evidence of osteoporosis of the lower extremities at the start of his study, thirteen months after injury. At the completion of his period of study there was no change in the degree of osteoporosis as measured by the densitometer. H. J. also had slight osteoporosis on starting studies and, in spite of the lowered urinary calcium excretion on the tilt table, the osteoporosis appeared to have definitely increased during the study. K. B., who on starting the study showed slight

osteoporosis at the lower ends of the tibia, was found to have bone atrophy developing in the mid-shaft of the tibia and, at the end of the study, progression of the process around the joint. L. B. showed no osteoporosis before or after the oscillating bed and tilt table. X-rays of A. S. were not satisfactory. Thus three of the four patients showed radiographic evidence of osteoporosis initially, and in two of these there was further progression, while in the third there was no apparent change.

2. Renal and bladder calculi: Patients M. L., K. B. and L. B. showed no evidence of calculi on x-ray examination during their studies. H. J. had one large and several smaller bladder but no renal calculi at the start of the study; x-rays at the end of the study period showed that the smaller stones had disappeared or had been passed while the large calculus was smaller, in spite of progressive changes in the long bones noted previously.

COMMENTS AND CONCLUSIONS

The results described would indicate that the metabolic alterations which occur following paraplegia cannot be ameliorated or prevented by imitation of ambulation by the oscillating bed or the upright posture (by means of the tilt table) when carried out as indicated.

In regard to calcium metabolism the oscillating bed used for a twelve-day period failed to alter the negative calcium balance, except in one patient (K. B.) in whom the relationship of the fall in urinary calcium to the use of the bed may have been coincidental. This negative response must be compared with the significant results in the subjects described by Whedon et al.14 Since their subjects were immobilized individuals who were otherwise in good health, it may well be that the added factors of trauma and paralysis in our patients contributed to the negative calcium balance in a quantitative or qualitative manner so that the oscillating bed was unable to exert any significant effect under these more severe circumstances. In addition, these investigators placed their subjects on the bed for five or six weeks, while our patients were so treated for only twelve days with the exception of M. L., whose period on the bed was double that length of time. This might account for the failure of response, although Whedon's subjects showed an effect after one week. Another difference lies in the fact that these investigators placed their patients on the oscillating bed immediately upon immobilizing them, while our subjects had been immobilized for at least one month. It is reasonable to conclude that more profound changes were permitted to occur in our subjects before the use of the bed than were allowed in their subjects, which might well account for our failure to produce an effect with the bed.

The results on the tilt table were no more encouraging than those on the oscillating bed. As has been mentioned, one patient (H. J.) showed a sharp fall in urinary excretion after six days on the tilt table, at a point when the maximum time on the table had been reached, but he failed to maintain this lowered, almost normal level for more than six days although his overall calcium balance on the table was less negative than during the control or oscillating bed periods. The significance of this fall is lessened perhaps by the fact that x-rays showed progression of the osteoporotic process rather than a regression. Another patient (K. B.) also showed low, almost normal levels of urinary calcium excretion on the tilt table but this had occurred while on the oscillating bed and particularly during the pyrexic period due to pyelonephritis. It should be pointed out that this marked reduction in both calcium and phosphorus excretion at the time of fever was not accompanied by any reduction in urinary volume. This patient also showed radiographic evidence of progression of osteoporosis of the lower extremities during his period of study. Particularly significant was the failure of the tilt table when used as early as one week after the onset of paraplegia in one individual (A. S.) to alter the already present hypercalcinuria. The failure of any response to this form of activity was emphasized by the fact that no change occurred in the urinary calcium excretion in this patient after the tilt table was discontinued. It might therefore be concluded that weight-bearing through the immobilized bones, when carried out in such patients for periods up to two hours per day, is ineffective in significantly altering the hypercalcinuria. This failure may perhaps be due to insufficient time of weight-bearing; however, it is not practical from the point of view of the nursing staff or patients to carry out this procedure for much longer periods each day.

Our results indicate that fecal calcium determinations are somewhat unreliable and that, as a result, the calcium balance is not as significant as the urinary calcium excretion in

determining the state of calcium metabolism. However, we were struck by the presence of a positive calcium balance in several of our patients, even when excreting excess amounts of calcium in the urine. This was most striking in

mobilized, eventually manage to compensate for their previous negative balance by retaining more of their ingested calcium than they would normally. This might be effected by a mechanism of increased gastrointestinal absorption.

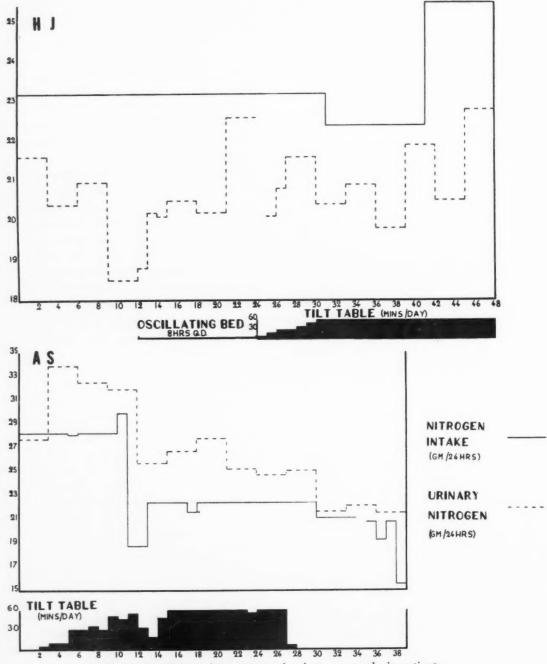
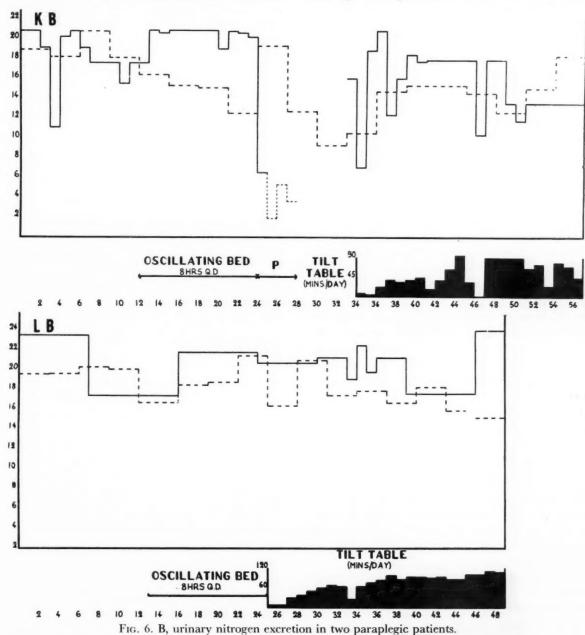


Fig. 6. A, urinary nitrogen excretion in two paraplegic patients.

M. L. whose lesion was the oldest (a little over one year) of any of those studied. He remained in positive balance for most of his study, although excreting some 300-350 mg./day of calcium in his urine. It might be postulated that such patients, even though still quite imThe observation that hypercalcinuria can occur in the presence of a positive balance seems to throw some doubt on the generally accepted assumption that hypercalcinuria in the immobilized individual is merely a reflection of depressed osteoblastic activity and/or increased osteoclastic activity. The hypercalcinuria under these circumstances might be explained on the basis of a renal factor, e.g., a failure of reabsorption of calcium by the renal tubular epithelium. More detailed study of renal tubular function

While some authors quoted in the review of the literature are of the opinion that nitrogen balance remains in a negative status for several months after cord injury, we were struck by our findings of equilibrium and even sometimes



in such a patient would help to elucidate this question.

The effect of the oscillating bed and tilt table on urinary phosphorus excretion was not notable with the exception of A. S. who, however, was also showing a progressive fall in nitrogen intake and excretion as well as a considerable loss of weight, since he was dying as a result of the neoplastic process present.

positive balance in three of the four patients studied. The only patient to show a marked negative balance was the subject with bronchial carcinoma; the presence of neoplasm would explain this protein loss readily. It would thus appear that paraplegic patients who have received adequate nutrition and who have few or no decubitus ulcers do not show any deviation from the catabolic response seen in other

660

injured or stressed individuals, attaining equilibrium or positive balance (anabolic phase) as soon as one month following injury. It is likewise evident that plasma protein levels remain within normal limits, except when there has been a history of poor nutrition as occurred in M. L. The oscillating bed and tilt table failed to affect nitrogen metabolism either favorably or unfavorably.

The observations of other investigators that serum calcium, phosphorus and alkaline phosphatase levels remain normal in paraplegia were confirmed in our study. The only deviation from normal was an elevated alkaline phosphatase in the patient with bronchial neoplasm, in whom such a rise might well be anticipated. Even though there was no gross evidence of liver or skeletal metastases, one must assume the presence of one or the other process in this individual.

The three patients studied in regard to renal function showed no abnormalities of the kidney other than slight albuminuria and a few white cells, and in one patient a bout of pyelonephritis. Since all these patients had been paraplegic for relatively short times, one might assume that measurable damage to the kidneys does not occur until later in the condition. The bacilluria is readily explainable on the basis of indwelling catheterization.

Studies of the basal metabolic rate did not reveal any significant abnormality.

The urinary 17-ketosteroid excretion was normal in the three patients studied except for one single low level in two and three low levels in one subject. Since none of the subjects showed evidence of the "demasculinization syndrome" clinically, and since the lower 17-ketosteroid levels were not constant features, these findings were not considered to be significant.

This study seems to indicate that in paraplegic patients the mechanisms responsible for the disuse osteoporosis would not appear to involve the lack of direct weight-bearing or circulatory changes in the lower extremities. Were such mechanisms primarily involved, one would expect to see more significant reduction of the urinary calcium excretion and perhaps some evidence of halting of demineralization when the tilt table or oscillating bed was employed. Of course, such a statement must always be qualified by consideration of the time factor and it is possible that these same procedures, when used for longer periods of time per day,

might prove effective in this regard. However, we believe that the primary factor responsible for the disuse osteoporosis, and thus the prime stimulus for normal osteoblastic activity, resides in the third possibility considered previously, i.e., muscular pulls and stresses. In flaccid paraplegia such muscular stresses are entirely absent and would be little if at all affected by the two procedures we have employed. On the other hand, patients with preponderantly spastic paraplegia would be expected to show little or no osteoporosis and a normal urinary calcium excretion. In support of this view are the results of an extremely brief study of one patient with spastic paraplegia who was not included in our study. This individual, R. R., forty-seven years of age, had a traumatic paraplegia at D1 of six months' duration, complicated by very severe spasticity of the lower extremities. With a calculated daily intake of 1,094 and 1,116 mg. calcium and a phosphorus intake of 1,621 and 1,068 mg. on two successive days, the urinary calcium was 126 and 120 mg., respectively. However, urinary creatinine values were only 0.82 and 0.69 gm. On another occasion, urinary calcium levels were 171 and 184 mg. day with creatinines of 0.69 and 0.74 gm./day. In spite of the low creatinine levels the normal urinary calcium excretion on a normal calcium intake appears significant and might indicate that the presence of spasticity is a crucial factor in determining the presence of hypercalcinuria and disuse osteoporosis, and that muscular contraction is the most important factor in "stresses and strains" on bone, stimulating osteoblastic activity. It should be pointed out, however, that one of our patients (L. B.) was partially spastic during his study, yet his urinary calcium levels were elevated. It might be practical to attempt galvanic contraction of flaccid muscles in paraplegic patients to bring about muscular contraction, but again the duration per day that this could be applied might prove to be a limiting factor. Another possibility would be the burying of a small inductance coil beneath the skin, with electrodes attached to the desired nerves. Such a procedure has been reported in one patient by Pool.13

SUMMARY

1. Paraplegia is followed by metabolic changes characterized by disuse osteoporosis, hypercalcinuria and negative nitrogen balance. The disuse osteoporosis has been postulated by Albright to be due to failure of osteoblastic activity, resulting from lack of "stresses and strains" on bone. Such "stresses and strains" might consist of direct weight-bearing through bone, circulatory changes in bone or muscular pulls on bone, acting either singly or in combination.

- 2. The metabolic changes, notably in calcium metabolism, of paraplegia have been found by Freeman to return to normal only upon ambulation, which is rarely possible before the fourth month after injury. An attempt was, therefore, made in five paraplegic patients to imitate ambulation while the patients were still immobilized by means of the oscillating bed, as suggested by Whedon et al., and by the tilt table. The effect of the oscillating bed was postulated to be via changes in circulation to the paralyzed extremities, while that of the tilt table was believed to act by direct weight-bearing through the bones of the lower extremities.
- 3. Calcium balance studies and roentgenographs failed to demonstrate any significant effect in our patients, either on the osteoporosis or hypercalcinuria, when these procedures were carried out for the durations of time specified. Studies of nitrogen metabolism revealed that anabolism or equilibrium was attained in all patients, provided adequate nutrition was available following injury. One patient with a lesion of thirteen months duration demonstrated a positive calcium balance in spite of concomitant hypercalcinuria. No significant effects on nitrogen or phosphorus metabolism, basal metabolic rate, renal function tests or urinary 17-ketosteroids were observed by use of the oscillating bed or tilt table.
- 4. The oscillating bed is of value in restoring the vasomotor tone of paralyzed extremities to normal
- 5. Direct weight-bearing through the lower extremities by means of the tilt table or other similar measures does not appear to be of value in affecting the calcium, phosphorus and nitrogen metabolism of the paraplegic patients.
- 6. It is postulated that the "stresses and strains" on bone might primarily result from muscular contractions rather than weight-bearing or circulatory changes.

Acknowledgments: The authors wish to express their deep gratitude to Dr. G. Gingras, Director

of the Paraplegic Unit, Queen Mary Veterans Hospital, for his cooperation in this study, also to Drs. J. S. L. Browne and A. H. Neufeld for their advice. Special thanks are due to the nursing, dietetic and laboratory staffs of the Clinical Investigation Unit, without whose aid this study would not have been possible.

REFERENCES

- Wyse, D. M. and Pattee, C. J. The metabolic alterations of immobilization, injury and paraplegia. D.V.A. Treat. Serv. Bull., 8: 63-77, 167-175, 217-226, 261-276, 351-358, 1953.
- COOPER, I. S., RYNEARSON, E. H., MACCARTY, C. S. and POWER, M. H. Metabolic consequences of spinal cord injury. J. Clin. Endocrinol., 10: 858, 1950.
- 3. Deitrick, J. E., Whedon, G. D. and Shorr, E. Effects of immobilization upon various metabolic and physiologic functions in normal men. Am. J. Med., 4: 3, 1948.
- HOWARD, J. E., PARSON, W. and BIGMAN, R. S., JR. Studies on patients convalescent from fracture.
 The urinary excretion of calcium and phosphorus. Bull. Johns Hopkins Hosp., 77: 291, 1945.
- FREEMAN, L. W. Metabolism of calcium in patients with spinal cord injuries. Ann. Surg., 129: 177, 1949.
- 6. Street, D. M. Treatment and rehabilitation of the paraplegic. Am. J. Surg., 80: 722, 1950.
- COVALT, D. A., COOPER, I. S., HOEN, T. I. and RUSK, H. A. Early management of patients with spinal cord injury. J. A. M. A., 151: 89, 1953.
- 8. CLARK, E. P. and COLLIP, J. B. A study of the Tisdall method for the determination of blood serum calcium with a suggestive modification. *J. Biol. Chem.*, 63: 461, 1925.
- Gomori, G. Modification of colorimetric phosphorus determination for use with photoelectric colorimeter. J. Lab. & Clin. Med., 27: 955, 1942.
- 10. Corley, R. C. and Denis, W. The determination of calcium in tissues, feces and milk. J. Biol. Chem., 66: 601, 1925.
- Callow, N. H., Callow, R. K. and Emmens, C. W. Colorimetric determination of substances containing grouping —CH₂CO— in urine extracts as indication of androgen content. *Biochem. J.*, 32: 1312, 1938.
- Schilling, A. and Lazlo, D. Rate of urinary calcium excretion following its intravenous administration as an indicator of bone metabolism. *Proc. Soc. Exper. Biol. & Med.*, 78: 286, 1951.
- POOL, J. L. Nerve stimulation in paraplegic patients by means of buried induction coil. J. Neurosurg., 3: 264, 1946.
- 14. Whedon, G. D., Deitrick, S. E. and Shorr, E. Modification of effects of immobilization upon metabolic and physiologic functions of normal men by use of an oscillating bed. *Am. J. Med.*, 6: 684, 1949.

An Abnormal Lipid-like Material and Carbohydrate in the Sera of Patients with Multiple Myeloma*

BERNARD A. SACHS, M.D., PAXTON CADY, B.S. and GEORGE ROSS, B.S.

New York, New York

with a metabolic abnormality was made over 100 years ago when Bence-Jones¹ first described the proteinuria which bears his name. Since then, three associated metabolic abnormalities—paramyloidosis,² abnormalities in serum proteins,³ cryoglobulinemia⁴—have been described.

During the course of a paper electrophoretic analysis of protein and lipid alterations in various disorders, we noted the two following abnormalities in the serum of a patient with multiple myeloma: (1) An abnormal lipid staining band in association with the abnormal globulin and (2) upon appropriate staining, an associated abnormal carbohydrate. The present report describes our findings in the sera of eleven patients with multiple myeloma which were analyzed both electrophoretically and chemically for protein, lipid and carbohydrate.

METHODS

Venous blood was drawn from eleven patients in the postabsorptive state with proved multiple myeloma. The separated sera were used for all electrophoretic and chemical analyses. Paper electrophoresis was performed with Flynn and de Mayo's⁵ modification of Durrum's apparatus, in which the filter paper strips are freely suspended in buffer troughs in a vapor-tight chamber. Adjacent electrode troughs are connected to the buffer troughs by wicks. Whatman No. 1 filter paper strips, 4 by 37.5 cm., were suspended in veronal buffer at a pH of 8.6 and an ionic strength of 0.1. The serum was streaked across the apex of the suspended filter paper with a micropipet; 0.0125 ml. was used for protein

and 0.025 ml. for lipid and carbohydrate. Constant voltage of 140 volts from a direct current power unit across seven strips for seventeen hours drew a current of 3.4 to 4 milliamperes. This provided sufficient time for migration and good separation of the protein fractions in the electrical field. The strips then were removed and dried in an oven at 105 to 110°F. for ten minutes to fix the protein by coagulation.

Naphthaline black 12B 200 was used for protein staining. The following ten staining dishes were used: the first with a saturated solution of the dye in 10 per cent acetic acid in methanol, the next eight with 10 per cent acetic acid in methanol to wash out the unbound dye and the last with methanol to remove the acetic acid. The strips remained ten minutes in each dish. This stain has a high affinity for protein and stains the protein bands a deep blue, leaving the background a very faint blue. The strips were stained for lipid in oil red 0 as described by Durrum.6 The lipids stain red against a pink background. Protein-bound carbohydrates were stained by Köiw's modification of the Hotchkiss histochemical method, using periodic acid and fuchsin sulfite.7 The carbohydrates stain violetred to purple with a very faint violet background.

The optical densities of the stained strips were read at 2 mm. intervals with a Photovolt No. 52-C densitometer using a 540 m μ filter. The protein curves were divided into their component fractions and the area of each fraction was measured with a compensating polar planimeter. Total protein was determined chemically by micro-Kjeldahl digestion followed by aeration and titration of the ammonia.^{8,9} Thus values for each protein fraction in grams were obtained.

* From the Medical Division, Montefiore Hospital, New York, N. Y. This study was supported in part by grants from the Lasdon Foundation, the National Institute of Arthritis and Metabolic Diseases of the United States Public Health Service and from the Medical Research and Development Board of the Surgeon General's Office.

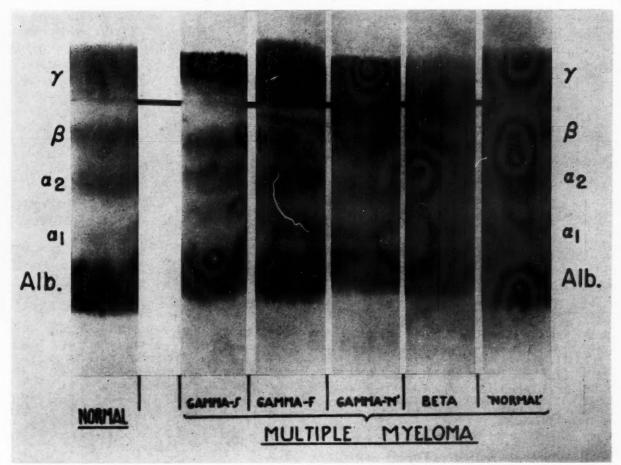


Fig. 1. Electrophoretic protein abnormalities in patients with multiple myeloma compared to the normal findings. The horizontal black line represents the point of application of the sera. Gamma-S = "slow" gamma myeloma; Gamma-F = "fast" gamma myeloma; Gamma-M = M component; Beta = beta myeloma; 'Normal' = minor anomalies (mild increases in the alpha globulins).

Total lipids were determined gravimetrically by extraction of the serum with Bloor's reagent. Aliquots of this extract were taken down to dryness in conical beakers on a hot plate. The dry residue was reextracted with four volumes of hot petroleum ether. The extracts were filtered through lipid-free cotton plugs into tared conical beakers, brought down to dryness, desiccated and weighed on an analytic balance.

Total and free cholesterol were determined by the Sperry and Webb¹⁰ modification of the Schoenheimer-Sperry method. The Zilversmit and Davis¹¹ method was used to determine lipid phosphorus. Total polysaccharides were determined chemically by the method of Graff et al.¹² and glucosamine by the method of West and Clark.¹³

RESULTS

1. Protein. Seven of the eleven sera revealed the characteristic electrophoretic pattern of gamma myeloma and two of beta myeloma. Two

showed only minor abnormalities. (Fig. 1.) Of the seven gamma myelomas, five were "slow," i.e., the abnormal gamma globulin migrated least and appeared at the beginning of the gamma band on the paper strip. (Fig. 4B.) One serum exhibited a "fast" gamma pattern, i.e., the abnormal gamma globulin migrated with the end of the gamma band closest to the positive electrode. (Fig. 4C.) The seventh gamma myeloma serum had a mobility which overlapped the gamma band to the area between gamma and beta (Fig. 4G.) The latter might be classified as the "M" component by Gutman;14 however, in the nomenclature of Reiner and Stern¹⁵ these sera are included in either the gamma or beta types of patterns.

In all but the two patients exhibiting minor electrophoretic abnormalities, the serum total proteins, as chemically determined, were elevated to values of 8.3 to 12 gm. per cent. In the patients with gamma myeloma, gamma globulin ranged from 31 to 59 per cent of the total protein

in contrast to the average normal value of 19.5 per cent. In the two patients with beta myeloma, the beta fraction was 46 and 57 per cent, as compared to the normal value of 13 to 14 per cent. The two sera with minor abnormalities

globulin) was found in one patient with beta myeloma and in one with the minor protein abnormalities. Although this pattern has not been seen by us in over 200 paper electrophoretic patterns stained for lipid, it has been noted on

TABLE I
PROTEIN FRACTIONS IN SERA OF PATIENTS WITH MULTIPLE MYELOMA

Subject		Total Protein		Albumin			Globulin									
No.	N	07	Gm.	CY		Alpha 1		Alpha 2		Beta		Gamma				
140.	Name	%	Gin.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm			
Normal*		100.0	7.6	49.1	3.7	6.5	0.5	10.6	0.8	14.3	1.1	19.5	1.5			
439	H. G.	101.1	10.5	31.2	3.3	4.5	0.5	7.2	0.8	11.1	1.2	47.1	4.9			
440	A. F.	99.7	10.2	28.7	2.9	6.5	0.7	9.3	1.0	10.1	1.0	45.1	4.6			
501	L. B.	100.8	11.1	30.0	3.3	9.0	1.0	8.5	0.9	12.8	1.4	40.5	4.5			
516	I. J.	100.8	10.3	31.4	3.2	5.9	0.6	9.2	0.9	9.6	1.0	44.7	4.6			
529	F. G.	101.0	8.3	30.9	2.6	5.4	0.4	12.2	1.0	14.4	1.2	38.1	3.2			
557	E. M.	99.9	9.5	42.1	4.0	6.4	0.6	11.1	1.1	9.1	0.9	31.2	3.0			
558	K. B.	100.4	12.0	24.2	2.9	4.3	0.5	5.2	0.6	7.8	0.9	58.9	7.1			
542	Н. В.	101.0	9.5	30.8	2.9	7.5	0.7	5.9	0.6	46.4	4.4	$\frac{8.5}{1.9}$	$\frac{0.8}{0.2}$			
547	J. L.	100.2	11.0	28.3	3.1	6.5	0.7	5.5	0.6	56.8	6.2	3.1	0.3			
512	I. G.	99.5	7.6	46.3	3.5	9.1	0.7	16.4	1.2	9.7	0.7	18.0	1.4			
559	M. B.	100.1	5.7	52.4	3.0	12.0	0.7	11.7	0.7	12.3	0.7	11.7	0.7			

^{*} The normal values represent the average values of five normal subjects. In subject H. B., the gamma globulin was subdivided into two fractions.

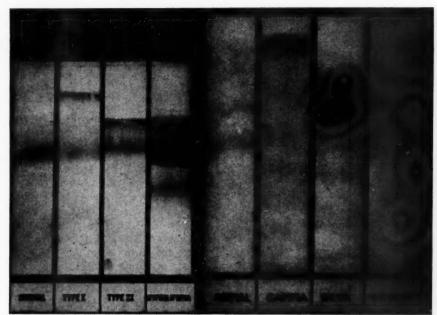
exhibited only small increases in alpha-1 and alpha-2 globulin, and in the one, a decrease in gamma globulin. (Table 1.)

2. Lipid. With the technic used, the normal electrophoretic lipid pattern is represented by a faint red band which extends from the point of application to or immediately beyond beta globulin where the intensity of color is sharply accentuated. (Figs. 2 and 3A.) An additional lipid staining band, with the mobility of the abnormal gamma globulin, was noted in five of the seven gamma myeloma sera. (Fig. 2, type 1.) These bands had a more orange tinge than the normal lipid bands and were more translucent than the remainder of the filter paper, hence could be seen better by reflected light than by transmitted light and did not record well in the densitometer. Another abnormality, arbitrarily designated type II (Fig. 2), in which a sharply accentuated lipid band is noted at the point of application (between beta and gamma

occasion by others in normal subjects. ¹⁶ The other sera exhibited no apparent lipid abnormality.

To ascertain whether any abnormality in serum lipid could be demonstrated chemically, total lipids, total and free cholesterol and lipid phosphorus were determined. (Table II.) Total lipids were elevated in two of the gamma myeloma sera and in one with only minor aberrations in protein pattern. These three also had increased levels of serum cholesterol and/or lipid phosphorus. In the two sera with beta myeloma and in one with gamma myeloma, cholesterol and lipid phosphorus were depressed.

Preliminary studies on the identification of the lipidstaining material: In an effort to characterize the abnormal lipid-staining material, the filter paper strips were extracted with Bloor's reagent (absolute alcohol, 3 parts; anhydrous ether, 1 part) before staining. When the filter paper strips were extracted with hot Bloor's reagent and then stained with oil red 0, all of the normal lipid



Lipid

Carbohydrate

Fig. 2. Paper electrophoretic patterns of lipid and carbohydrate in sera from patients with multiple myeloma compared to a normal subject and a patient with essential hyperlipemia. The normal carbohydrate bands stain a faint violet-red which unfortunately does not reproduce well in black and white. The carbohydrate pattern in the patient with hyperlipemia is normal. The lipid and carbohydrate anomalies found in the patients with myeloma are shown in the two center strips of each group.

and the "type II" anomaly were completely removed. However, the bands associated with the abnormal globulin still stained for lipid. Indeed, in the beta myeloma sera and in the two "fast" gamma myeloma sera, abnormal lipid-

TABLE II SERUM LIPIDS IN PATIENTS WITH MULTIPLE MYELOMA

Patient	Age	Electroph	oresis	Total Lipids	Cholest (mg.	Lipid Phos-		
	Sex	Protein	Lipid	(mg. %)	Total	Free	phorus (mg. %	
Normal		N	N	600-1,000	150-300		6-10	
L. B.	42, F	Gamma-S	N	631	173	53.5	8.5	
I. G.	50, M	N	11	1,444	323	95.4	13.7	
I. J.	50, M	Gamma-F	I	588	158	42.5	10.6	
Н. В.	68, M	Beta	N	606	84	19.0	4.8	
J. L.	55, M	Beta	11	669	103	32.2	5.4	
A. F.	62, F	Gamma-S	1	1,094	269	67.5	13.5	
E. M.	75, M	Gamma-S	I	919	203	53.4	9.9	
K. B.	50, F	Gamma-F	N	631	150	40.8	10.4	
M. B.	46, M	N	N	550	167	43.3	7.7	
H. G.	55, M	Gamma-S	I	504	116	26.8	5.2	
F. G.	70, F	Gamma-S	1	1,131	338	83.4	10.3	

staining bands, previously masked by the normal lipid, became evident. Thus after Bloor's extraction the only strips which did not show an abnormal lipid-staining band were those prepared with sera showing but minor protein abnormalities.

3. Carbohydrate. The normal electrophoretic carbohydrate pattern consists of light violet-red staining bands which correspond to the protein bands. (Fig. 3A.) Carbohydrate, ab-

TABLE III
CARBOHYDRATES IN SERA OF PATIENTS WITH MULTIPLE
MYELOMA

Patient	Age	Electro	phoresis	Total	Glucosamine (mg. %)	
ratient	Sex	Protein	СНО	Polysaccharides (mg. %)		
Normal		N	N	120-155	80-110	
L. B.	42, F	Gamma	Gamma	255	225	
I. G.	50, M N		N	158	124	
I. J.	56, M	Gamma	Gamma	164	149	
H. B.	68, M	Beta	Beta	252	224	
J. L.	55, M	Beta	Beta	415	417	
A. F.	62, F	Gamma	Gamma	162	186	
E. M.	75, M	Gamma	Gamma	156	144	
K. B.	50, F	Gamma	Gamma	353	346	
M. B.	46, M	N	N	126	119	
H. G.	55, M	Gamma	Gamma	168	145	
F. G.	70, F	Gamma	Gamma	168	142	

normal in position and increased in amount, was invariably found with abnormal myeloma protein, whether gamma or beta. These bands stained deep purple. (Fig. 2.) Only the two sera with minor protein anomalies revealed no abnormal carbohydrate.

This abnormality was always associated with



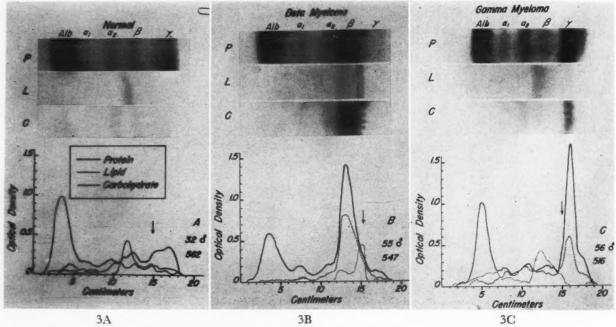


Fig. 3. Protein (P); lipid (L); carbohydrate (C). Interrelationships of normal serum (A) compared with beta myeloma (B) and gamma myeloma (C). The optical density of each strip is recorded below. The arrows indicate the points of application of the sera.

an increase in chemically determined total polysaccharides or glucosamine. (Table III.) In four sera there was a twofold or threefold increase in both these fractions to levels never before obtained in this laboratory. Of five others which had a moderate increase in glucosamine, four had a slight rise and one no elevation in total polysaccharides. The two sera with minor protein changes had high normal values for glucosamine and one showed a high normal value for total polysaccharides.

COMMENTS

Protein. Designating myeloma sera as alpha, beta or gamma implies only that there is a similarity between the electrophoretic mobilities of abnormal and normal serum components and does not necessarily indicate chemical identity. The electrophoretic gamma and beta peaks in multiple myeloma sera are much sharper than the peaks found in either normal sera (Fig. 4) or in hyperglobulinemic sera in other disorders. Immunologic and chemical differences between the beta and gamma globulins of myeloma and of normal sera also exist. 17

In sera from ninety-one myeloma patients Reiner and Stern¹⁵ found 6.6 per cent alpha patterns, 15.4 per cent beta patterns, 56 per cent gamma patterns and 22 per cent minor anomalies. That the hyperglobulinemia is most often due to the gamma fraction and less fre-

quently the beta fraction is confirmed by our relatively small series, as well as by others. 17,18 Alpha myeloma is rarely seen. The patients did not exhibit Bence-Jones proteinuria during this study. One patient with gamma myeloma (E. M.) was reported to have Bence-Jones proteinuria while at another institution.

Lipid. Since the beta fraction contains most of the lipoproteins, marked lipemia might be expected when this fraction is increased. Despite the fact that an increased beta fraction occurs principally in myeloma and in primary biliary cirrhosis, 19 a characteristic lipemia occurs only in the latter. Waldenström, 18 who has had a wide experience with myeloma, observed only one case with an increased beta fraction and marked lipemia. Hartman²⁰ noted a moderate increase in cholesterol in beta myeloma. In the serum of a patient with myeloma, Hill et al.21 described the presence of a lipoprotein, a "cryoprotein" which solidified on cooling. When it was purified by repeated reprecipitation, needle-like crystals of cholesterol esters separated out after three days. Aside from these, no other study of the lipid metabolism in multiple myeloma has been reported.

It is of interest that both our patients with beta myeloma (H. B. and J. L.) and one with gamma myeloma (H. G.) showed decreased values for serum cholesterol and lipid phosphorus. This did not correlate with the patients' nutritional

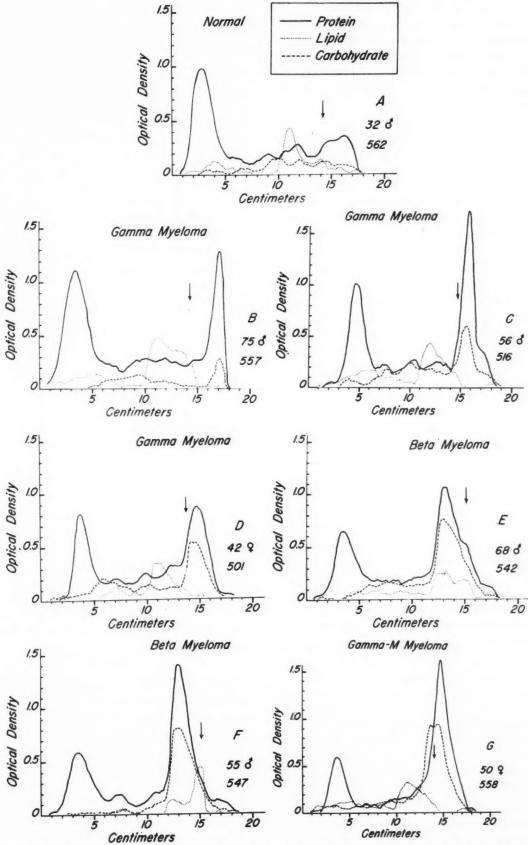


Fig. 4. Protein-lipid-carbohydrate interrelationships of a normal serum compared with the various types of multiple myeloma.

status since one (H. B.) was obese. It is of note that three of eleven patients exhibited hyperlipemia associated with an increase in cholesterol and/or lipid phosphorus. These chemically determined abnormalities could not be qualitatively correlated with an electrophoretically determined lipid anomaly.

Five of the seven gamma myeloma sera exhibited a lipid-staining band associated with the abnormal protein. Of interest is the finding that other lipid-staining bands which were masked by overlapping normal lipid became apparent when the normal lipid was removed by extraction with Bloor's reagent. Preliminary studies in the identification of the abnormal lipid staining bands make it doubtful that this material is true fat. Clarification of this point must await completion of studies now in progress.

Carbohydrate. The physiologic role, metabolism and chemistry of the serum polysaccharides are largely unknown despite the fact that they are quantitatively important constituents of blood. One fraction, seromucoid, has been found to be composed of acetylglucosamine, mannose and galactose. Serum polysaccharides and glucosamine have been found to be increased in the presence of sterile abscesses, bacterial infections, fever, nephritis, diabetic glomerulosclerosis, vascular disease secondary to diabetes, rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus, tuberculosis, late pregnancy and cancer.22-26 When specifically investigated, it has been found that the polysaccharide associated with albumin and alpha globulin is elevated. Except for one report of Boas and Reiner,27 later refuted by Ehrich,22 in which a correlation was noted between glucosamine and gamma globulin in patients with disseminated lupus erythematosus, polysaccharides have not heretofore been reported to be increased in the gamma globulin fraction. It appears that the polysaccharide content of the albumin fraction is elevated in cases in which tissue proliferation occurs; when the process involves fever, the polysaccharide content of the alpha globulin also increases. The polysaccharide abnormality in our patients with multiple myeloma differs from the above disorders both qualitatively and quantitatively. The levels of both total polysaccharide and glucosamine reached by some of the patients with myeloma are the highest recorded in this

Greenspan et al.²⁶ chemically estimated the polysaccharides of whole serum, the polysac-

charides of the serum proteins and the polysaccharide and protein components of the serum mucoprotein in patients with advanced cancer, in normal subjects, in patients with parenchymatous liver disease and in six patients with myeloma. They found that the carbohydrate/ protein ratios of the myeloma group were consistently elevated when compared with the advanced cancer group. This elevation was due to a decrease in the protein content of the serum mucoprotein while the polysaccharide remained at normal levels. The same finding was noted in patients with hepatic insufficiency but could not be attributed to the presence of hyperglobulinemia or selective co-precipitation of the protein moiety of the mucoprotein.

The anomalous carbohydrate invariably found with abnormal protein in the present series of patients apparently represents a heretofore unrecognized metabolic abnormality in multiple myeloma. Mucopolysaccharides are found normally in ground substance, fibers and basement membrane. Paramyloid, found frequently in patients with multiple myeloma, is believed by some²⁸ to be produced by the abnormal plasma cells. Amyloid and paramyloid consist of protein and mucopolysaccharide. One of the important constituents of mucopolysaccharide is glucosamine. It is possible that the abnormal carbohydrate found in association with the abnormal protein is mucopolysaccharide and that this is chemically reflected by the observed increase in glucosamine. Proof of this must await further study.

The abnormal protein, lipid and carbohydrate are apparently bound and migrate together electrophoretically. The protein-lipid-carbohydrate complex may be elaborated by the myeloma cell but proof of this must await further study.

SUMMARY

Sera from eleven patients with multiple myeloma were separated by paper electrophoresis and differentially stained for protein, fat and carbohydrate. Of the eleven, seven revealed protein patterns of gamma myeloma and two of beta myeloma; two exhibited minor abnormalities.

In five of the seven with gamma myeloma an abnormal lipid-staining band which migrated with gamma globulin was present. In one with beta myeloma and one with minor anomalies a lipid band was found between beta and gamma globulin. Extraction of the filter paper with Bloor's reagent removed the normal lipids and

the bands between beta and gamma globulin. This revealed four other, previously masked, lipid-staining bands associated with abnormal protein. Only the two sera with minor protein anomalies showed no abnormal lipid after extraction.

Total lipids, chemically determined, were elevated in only two gamma myeloma sera and in one with normal protein pattern. These three also had increased levels of serum cholesterol and/or lipid phosphorus. In two with beta myeloma and one with gamma myeloma, cholesterol and lipid phosphorus levels were depressed.

Carbohydrate, abnormal in position and increased in amount, was invariably found with abnormal protein, whether gamma or beta. This was always associated with an increase in chemically determined total polysaccharides or glucosamine. In four sera both these fractions were two to three times normal values. Five others had a moderate increase in glucosamine; four of these had a slight rise and one no elevation in total polysaccharides. The two with minor protein abnormalities had no abnormal carbohydrate, electrophoretically or chemically.

This increase in serum polysaccharides of patients with multiple myeloma differs from that found by others in patients with carcinoma in that it is associated with the abnormal globulin rather than albumin.

Acknowledgments: We wish to thank Drs. Daniel Laszlo, Herta Spencer, Samuel Melamed, Isaac Lewin, Helen Horowitz and Marian Isaacs for making their patients with multiple myeloma available for study, and Mr. Antol Herskovitz for the photographs. Drs. Louis Leiter and Raymond E. Weston offered encouragement and most helpful criticism.

REFERENCES

- Bence-Jones, H. On a new substance occurring in the urine of a patient with "mollities ossium." Phil. Tr. Royal Soc., London, p. 55, 1848.
- 2. Adams, W. and Dowse, T. S. Mollities ossium. Tr. Path. Soc., London, 23: 186, 1872.
- Longsworth, L. G., Shedlovsky, T. and McInnes, D. A. Electrophoretic patterns of normal and pathological human blood serum and plasma. J. Exper. Med., 70: 399, 1939.
- Lehman, J. and Flemberg, T. Discussion. Nord. med., 23: 1565, 1944.
- FLYNN, E. V. and DE MAYO, P. Micro-electrophoresis of protein on filter-paper. *Lancet*, 2: 235, 1951.
- Durrum, E. L., Paul N. H. and Smith, E. R. B. Lipid detection in paper electrophoresis. Science, 116: 428, 1952.
- 7. Körw, E. Staining of protein-bound carbohydrates

- after electrophoresis of serum on filter paper. Scandinav. J. Lab. & Clin. Invest., 4: 244, 1952.
- Reith, J. F. The collection of ammonia-containing distillate in boric acid solution in clinical chemical work. *Chem. Zentralbl.*, 1: 242, 1942.
- 9. Howe, P. E. The determination of protein in blood—a micro method. *J. Biol. Chem.*, 49: 109, 1921.
- SPERRY, W. M. and WEBB, M. A revision of the Schoenheimer-Sperry method for cholesterol determination. J. Biol. Chem., 187: 97, 1950.
- 11. ZILVERSMIT, D. B. and DAVIS, A. K. Microdetermination of plasma phospholipids by trichloracetic acid precipitation. J. Lab. & Clin. Med., 35: 155, 1950.
- 12. Graff, M. M., Greenspan, E. M., Lehman, I. R. and Holechek, J. J. Estimation of nonglucosamine polysaccharides of the serum proteins with the anthrone reagent. J. Lab. & Clin. Med., 37: 736, 1951
- 13. West, R. and Clark, D. H. The concentration of glucosamine in normal and pathological sera. J. Clin. Investigation, 17: 173, 1938.
- 14. GUTMAN, A. B. The plasma proteins in disease. Advances in Protein Chemistry, 4: 156-250, 1948.
- REINER, M. and STERN, K. G. Electrophoretic studies on the protein distribution in the serum of multiple myeloma patients. Acta haematol., 9: 19, 1953
- 16. ENGLE, R. Personal communication.
- SNAPPER, I., TURNER, L. B. and Moscovitz, H. L. Multiple Myeloma. New York, 1953. Grune & Stratton, Inc.
- 18. WALDENSTRÖM, J. Abnormal proteins in multiple myeloma. Advances Int. Med., 5: 398, 1952.
- Ahrens, E. H., Payne, M. A., Kunkle, H. G., Eisenmenger, W. J. and Blondheim, S. H. Primary biliary cirrhosis. Medicine, 29: 299, 1950.
- HARTMAN, F. Beitrag zur Kenntnis des Verhaltens von Serum und Urineiweiss beim Plasmacytom. Deutsches Arch. f. klin. Med., 196: 161, 1949.
- HILL, R. M., MULLIGAN, R. M. and DUNLOP, S. G. Plasma cell myeloma associated with a high concentration of plasma lipoprotein. Am. J. Path., 24: 689, 1948.
- 22. Ehrich, W. E. Nature of collagen diseases. *Am. Heart J.*, 43: 121, 1952.
- 23. Shetlar, M. R. The polysaccharides of serum proteins in cancer. Texas Rep. Biol. & Med., 10: 228, 1952.
- SHETLAR, M. R., SHETLAR, C. L., RICHMOND, V. and EVERETT, M. R. The polysaccharide content of serum fractions in carcinoma, arthritis and infections. Cancer Research, 10: 681, 1950.
- Berkman, J., Rifkin, H. and Ross, G. The serum polysaccharides in diabetic patients with and without degenerative vascular disease. J. Clin. Investigation, 32: 415, 1953.
- 26. Greenspan, E. M., Lehmann, I., Graff, M. M. and Schoenbach, E. B. A comparative study of the serum glycoproteins in patients with parenchymatous hepatic disease or metastatic neoplasia. *Cancer*, 4: 972, 1951.
- 27. Boas, N. F. and Reiner, M. Effect of ACTH and cortisone on serum hexosamine and gamma globulin levels in acute disseminated lupus erythematosis. J. Clin. Endocrinol., 11: 890, 1951.
- 28. Magnus-Levy, A. Multiple myeloma. Acta med. Scandinav., 95: 218, 1938.

Serum Proteins and Lipoproteins in Multiple Myelomatosis*

Lena A. Lewis, M.D. and Irvine H. Page, M.D. Cleveland, Ohio

The serum proteins of patients with multiple myelomatosis have been extensively studied 1-4 but investigation specifically of the lipoproteins apparently has not been made. The bizarre protein patterns in this disorder suggested that the lipoproteins might also show anomalies. Accordingly, studies were made of the serum of twenty-four patients with multiple myeloma, established by the usual clinical criteria and by bone marrow examination. Four of these also had arteriosclerotic heart disease as demonstrated by autopsy in two instances and by clinical findings in two others.

METHODS

Electrophoretic analysis of serum proteins made by Longsworth's⁵ modification of the Tiselius electrophoretic technic, using barbiturate buffer, pH 8.6, ionic strength 0.10 μ. Serum total protein was determined by the biuret method⁶ and cholesterol by the method of Abell et al.⁷ Lipoproteins were studied by ultracentrifugation at a density of 1.21 by Lewis, Green and Page's⁸ modification of Gofman's technic.⁹

In addition to the twenty-four patients with multiple myelomatosis, data were obtained in one person with plasma cell myeloma of sacrum and radius, one with lymphosarcoma of the bone marrow, and one with benign purpura-hypergammaglobulinemia observed for nine years.

RESULTS

Electrophoretic analysis of the serum was performed in twenty-one of the twenty-four patients with multiple myelomatosis. In four patients a high concentration was found of material with electrophoretic mobility between that of β and γ_2 -globulin, originally designated in the literature 1 as "M-globulin" but now classified

as γ_1 -globulin. ^{10,11} Increased concentrations of β -globulin occurred in four cases. Eleven exhibited large γ_2 -globulin peaks. Two showed no unusual changes. (Table I.) In one serum (Case 3) some precipitation occurred in the descending channel in the γ_2 -globulin area, suggesting that the protein was a cryoprotein. No precipitation was observed in any of the other sera either when stored in the cold or during electrophoresis. The sera of the patient (Case 25) with plasma cell myeloma of sacrum and radius, and of the one (Case 27) with lymphosarcoma of the bone marrow, both showed elevated concentration of material with the electrophoretic mobility of γ_2 -globulin.

Hypergammaglobulinemia was present for at least nine years in one patient (Case 26), the γ_2 -globulin being 3.8 gm. per 100 ml. in 1944 and 6.5 gm. in 1953.

The lipoprotein pattern of patients with multiple myelomatosis showed all of the components present in normal sera, -S > 70, 40-70, 25-40, 20-25 and 1-10. (Table I.) The concentration of the low density -S > 70, and 40-70, and of -S 20-25 was only slightly beyond the range for normal human subjects of similar age, averaging 53, 41 and 12 mg. per 100 ml., respectively; the corresponding figures for normal subjects are 41, 31 and 13. The concentration of -S 25-40 and -S 1-10 was significantly lower in myeloma sera, averaging 131 and 97 mg. per 100 ml., respectively, as compared with the normal average of >190 mg. and 192 mg. per 100 ml.

The serum cholesterol concentration of patients with multiple myelomatosis was consistently low, averaging 131 mg. per 100 ml.; that of normals of similar age (forty-five to seventy years) was 237 mg. per 100 ml. (Table I.) In some cases low concentrations are known to

^{*} From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

have existed for years. Thus, determinations made thirteen months apart in Case 2 showed 76 and 67 mg. per 100 ml.; those made three years apart in Case 10 were 133 and 123 mg. per 100 ml.; and those made eight months apart in Case 3 were 183 and 168 mg. per 100 ml. and the -S 1–10 component is not present in the lipoprotein concentrate.

Electrophoretic analysis of lipoproteins concentrated at a density of 1.21 showed -S 40-70 to have a mobility similar to γ_1 -globulin; -S 25-40 has a mobility corresponding to

TABLE I

Case	Age	Total Serum Protein (gm./100 ml.)	Abnormal Serum Component		Serum Cholesterol	Serum		roteins 100 m		Evidence of Arteriosclerosis, Kidney Involvement and		
No.	Sex		Mobility Similar to	(gm./100 ml.)	(mg./100 ml.)	-S < 70	40-70	25-40	20-25	1-10	Other Spe	ecial Notes
1	65. M	10.52	γ₂-globulin	6.46	76	20	<5	59	5	107	ASHD III	
2	57, M	9.25	γ2	2.59	183	94	63	188	24	118	Arteriosclerosis, and coronary	
3	60, M	7.68	7:	2.72	120	0	23	186	<5	56	ASHD iv	
4	63, F	8.10	No abnormality		145	34	29	143	<5	130	Arteriosclerosis,	moderate, gen , atherosclerosi
5	65, M	6.61	ß	2.41	93	22	31	59	<8	140	Aorta: moderate miliary tuberce	
6	61, F	9.50	β	5.31	174	97	71	154	12	201		
7	60, F	11.46	72	6.79	135	42	47	152	12	94		
8	65. M	7.65	В	1.95	187	94	66	164	14	106	Renal insufficien	
9	67. M	13.00	β	8.48	45	12	12	63	<7	24	Renal insufficien	
10	55, M	11.40	71	7.50	123	<5	22	140*				
11	67, M	8.95	71	2.13	124	36	31	142	9	95		
12	47, M	11.75	γ1	7.61	92	35	30	106	14	70		
13	61, M	12.34	71	7.15	104	59	43	59	24			
14	53, M	8.00	71	2.68	142	39	42	104	<5	86		
15	53, M	9.54	71	4.50	142	58	33	141	14	52		
16	64, F	11.99	γ2	8.10	80	16	33	78	<5			
17	47, M	11.65	72	6.54	119	28	31	130	5	71		
18	52, F	10.80	72	3.18	177	14	38	212	9	129		
19	70, F	12.75	72	7.19		71	123	212	14		Renal insufficier	
20	59. F	7.57	72	2.20	162	13	13	182	16	156	Renal insufficien	
21	53, M	8.60	No abnormality		156	118	80	141	14	70	"Myeloma kidn	
22	61. M	7.75	γ2	2.24	204	16	45	200	28	152		
23	49. F				163	296	36	41	30	178		
24	69. M				198	59	61	199	21	164	Renal insufficier	
25	55, M	8.10	γ2	2.79	153	24	35	152	42		Plasma cell mye	eloma of sacrun
26	F	9.85† 12.60‡	γ2 γ2	3.78 6.53	165	47	54	190	11	90	Benign purpura globulinemia	; hypergamma
27	M	9.40	γ2	3.57	128	28	24	106	12	124	Lymphosarcoma	a of bone
				A	verage Normal V	alues						
				Cholesterol		-S < 7	70	40-	70	25-4	40 20-25	1-10
35-60 F 35-60 M		\bar{X}. ± \\ \bar{X}. ±	\overline{X} . \pm S.E. 230.4 \pm 8.9 \overline{X} . \pm S.E. 242.4 \pm 3.0		22.0 ± 59.5 ±		29.1 ± 32.7 ±		>18		228.1 ± 11.6 155.8 ± 4.8	

* Density used 1.063.

† Date of determination, March 8, 1944. ‡ Date of determination, March 17, 1953.

Repeated electrophoretic and lipoprotein studies showed a relatively stable pattern.

COMMENTS

The lipoproteins, when measured at a density of 1.21, and identified by their -S values as -S > 70, 40–70 and 24–50, correspond respectively to S_t 20-100+, 12-20 and 3-8 as classified by Gofman from studies at a density of 1.063. When the Gofman procedure is employed, the -S 20–25 component is only poorly resolved β_1 -globulin; -S 20-25 a mobility of α_2 -globulin, and -S 1–10 a mobility of α_1 -globulin. The -S > 70 components moved only slightly and were poorly resolved in boundary electrophoresis.

The changes in the serum electrophoretic protein pattern did not correlate closely with the lipoprotein pattern or the serum cholesterol concentration. Sera with the greatest increase in total protein concentration usually had low concentrations of -S 25–40, i.e., β -lipoprotein.

Low serum cholesterol with high γ_2 -globulin concentration was frequently observed. In a group of twenty-nine patients suffering from a variety of diseases such as arthritis, hepatitis, sarcoidosis, and showing serum γ_2 -globulin levels greater than 2.00 gm. per 100 ml., the cholesterol was less than 200 in nineteen and of these, less than 175 mg. per 100 ml. in fifteen instances. Those having both high γ_2 -globulin and high cholesterol concentrations were chiefly hypertensives and diabetics.

The occurrence of very low concentrations of lipoproteins, especially β -lipoprotein, -S 25–40, in sera of patients No. 5, 6, 8 and 9, with a high concentration of β -globulin, excludes the possibility that the increase in β -globulin is due to large amounts of lipoproteins. Evidently it is the non-lipoprotein part of the β -globulin complex which increases under these circumstances.

Putnam and Udin¹⁰ observed, as we have found in the present series, that most myeloma proteins have a mobility in the range of normal γ -globulins. The finding of different end-groups in some of the purified myeloma proteins from those in normal γ -globulins suggested that "an aberration in protein synthesis occurs in this disease." ¹²

Of four myeloma sera all of the γ -globulin type, studied by Nikkilä¹³ by paper electrophoresis, three showed very low α_1 -lipoprotein concentration, and elevated α_2 and β -lipoprotein values. The cholesterol concentration in two was elevated. Neither the total serum protein nor γ -globulin concentration was given.

The low concentration of cholesterol and of β -lipoprotein (-S 25-40) and α_1 -lipoprotein (-S 1-10) cannot be explained on the basis of caloric restriction or weight reduction, for a few of our patients who had the lowest cholesterol concentrations (Cases 12, 16 and 17) were obese. Decreased concentrations of cholesterol and low density lipids have been observed during periods of restricted caloric intake and weight reduction. ¹⁴

The finding of low serum lipoprotein and cholesterol and a large component with electrophoretic mobility of γ_2 -globulin in the serum of patient No. 27 with lymphosarcoma of the bone marrow indicates that the lymphocyte as well as the plasma cell may be involved in the changed lipid and protein patterns.

The highest serum lipoprotein concentrations were observed in the patients with myeloma and renal insufficiency but even in these instances the concentrations were not higher than normal. These findings contrast with those in patients in the nephrotic phase of nephritis or with malignant hypertension with renal involvement, in whom the lipoproteins, especially the -S 20–25 and -S 25-40 and low density components are greatly increased16 and the serum cholesterol is usually above 300 mg. per 100 ml. In myelomatosis renal insufficiency may result from protein precipitates chiefly in the proximal tubules.3,17 The difference in site and amount of protein deposits in myelomatosis and nephritis, which are probably due to difference in urinary protein solubility, might be a factor in the abnormal lipoprotein patterns.

Two cases of α -globulin plasmacytoma have been reported. In one the α_2 -globulin was 53.2 per cent of the total protein and the serum cholesterol was only 160 mg. per cent, thus eliminating the possibility that the abnormal component was lipoprotein. Lohss et al. In also failed to find any evidence that the abnormal component of patients with the α or β type disease was lipoprotein.

Repeated plasma and bone marrow studies in multiple myeloma patients receiving urethane have shown a parallelism between the concentration of abnormal plasma proteins and the number of plasma cells in the bone marrow, 20,21 providing additional evidence that the plasma cell is the source of the abnormal protein in myeloma. The abnormal serum proteins had the electrophoretic mobility of γ_1 - or γ_2 -globulin.

SUMMARY

The serum lipoprotein pattern of twenty-four patients with multiple myelomatosis studied by ultracentrifugation showed the concentrations of -S > 70, 40-70 (γ_1 -globulin) and -S 20–25 (α_2 -lipoprotein) components to be normal. Lower than normal values were found for -S 25–40 (β_1 -lipoprotein) and -S 1–10 (α_1 -lipoprotein). Serum cholesterol concentrations also were lower than those of normal people of like age and sex. Four of these patients had arteriosclerotic heart disease and six had marked renal insufficiency.

The electrophoretic protein patterns showed increased concentrations of components with mobility of β_1 -, γ_1 - or γ_2 -globulin. There was no correlation between the changes of lipoprotein

AMERICAN JOURNAL OF MEDICINE

and electrophoretic protein patterns, although those sera showing the largest globulin concentrations usually had very low β_1 - and α_1 -lipoproteins and cholesterol.

Acknowledgment: We want to thank Dr. John D. Battle, Jr., Division of Medicine, and Dr. G. S. Phalen, Division of Surgery, for their cooperation in making the patients available for study. The technical assistance of Stephen Barany, Louise P. Crouter and Joanna Jones is also gratefully acknowledged.

REFERENCES

- MOORE, D. H., KABAT, E. A. and GUTMAN, A. B. Bence-Jones proteinemia in multiple myeloma. J. Clin. Investigation, 22: 67, 1943.
- 2. Keckwick, R. A. The serum proteins in multiple myeloma. *Biochem. J.*, 34: 1248, 1940.
- BLACKMAN, S. S., JR., BARKER, W. H., BUELL, M. V. and DAVIS, B. D. On the pathogenesis of renal failure associated with multiple myeloma. Electrophoretic and chemical analysis of protein in urine and blood serum. J. Clin. Investigation, 23: 163, 1944
- Lewis, L. A., Bortz, D. W. and Battle, J. D., Jr. Electrophoretic and ultracentrifugal analysis of serum proteins in multiple myeloma. *Cleveland Clin. Quart.*, 18: 119, 1951.
- Longsworth, L. G. A modification of the schlieren method for use in electrophoretic analysis. J. Am. Chem. Soc., 61: 529, 1939.
- Sols, A. An improved biuret reaction of proteins and the two-standard colorimetry. Nature, 160: 89, 1947.
- ABELL, L. L., LEVY, B. B., BRODIE, B. B. and KEN-DALL, F. E. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem., 195: 357, 1952.
- Lewis, L. A., Green, A. A. and Page, I. H. Ultracentrifugal lipoprotein pattern of serum of normal, hypertensive and hypothyroid animals. Am. J. Physiol., 171: 391, 1952.
- GOFMAN, J. W., LINDGREN, F., ELLIOTT, H., MANTZ, W., HEWITT, J., STRISOWER, B. and HERRING, V.

- The role of lipids and lipoproteins in atherosclerosis. Science, 111: 166, 1950.
- PUTNAM, F. W. and UDIN, B. Proteins in multiple myeloma. Physicochemical study of serum proteins. J. Biol. Chem., 202: 727, 1953.
- ALBERTY, R. A. A study of the variation of the average isoelectric points of several plasma proteins with ionic strength. J. Phys. & Colloid Chem., 53: 114, 1949.
- PUTNAM, F. W. N-terminal groups of normal plasma globulins and myeloma proteins. Federation Proc., 13: 277, 1954.
- Nikkilä, E. Studies on the lipid-protein relationship in normal and pathological sera and the effect of heparin on serum lipoproteins. Scandinav. J. Clin. & Lab. Invest., Suppl., 5: 8, 1953.
- WALKER, W. J., LAWRY, E. Y., LOVE, D. E., MANN, G. V., LEVINE, S. A. and STARE, F. J. Effect of weight reduction and caloric balance on serum lipoprotein and cholesterol levels. Am. J. Med., 14: 654, 1953.
- PAGE, I. H. Atherosclerosis. An introduction. Circulation, 10: 1, 1954.
- Lewis, L. A. and Page, I. H. Electrophoretic and ultracentrifugal analysis of serum lipoproteins of normal, nephrotic and hypertensive persons. Circulation, 7: 707, 1953.
- BLACKMAN, S. S., JR. and DAVIS, B. D. Electrophoretic and Kjeldahl analysis of protein in nephritic urine and the effect of proteinuria on the human kidney. South. M. J., 36: 247, 1943.
- 18. Wuhrman, V. F., Wunderly, C. and Wiedemann, E. Ueber das Alpha-Globulin-Plasmacytom. Schweiz. med. Wchnschr., 8: 180, 1948.
- Lohss, F., HILLMANN-ELIES, A. and HILLMANN, G. Plasma proteins in myeloma. II. The physical and chemical nature of the alpha and beta globulins in myeloma. Ztschr. f. Naturforsch., 80: 619, 1953.
- Rundles, R. W., Dillon, M. J. and Dillon, E. S. Multiple myeloma. III. Effect of urethane therapy on plasma cell growth, abnormal serum protein components and Bence-Jones proteinuria. J. Clin. Investigation, 29: 1243, 1950.
- RUNDLES, R. W., COOPER, G. R. and WILLETT, R. W. Multiple myeloma. IV. Abnormal serum components and Bence-Jones protein. J. Clin. Investigation, 30: 1125, 1951.

Disappearing Bones: A Rare Form of Massive Osteolysis*

Report of Two Cases, One with Autopsy Findings

L. W. GORHAM, M.D., † A. W. WRIGHT, M.D., H. H. SHULTZ, M.D. and F. C. MAXON, JR., M.D. Albany, New York

THE gradual and often complete resorption of a bone or group of bones is an unusual phenomenon. It has been described under various titles such as phantom clavicle, acute absorption of bone and disappearing bone. Occurring chiefly in young adults and frequently first discovered after some sort of injury, often a fracture, the slow dissolution ultimately results in complete disappearance of the affected bone or bones. Although we have been able to find sixteen reported cases, some of them very well documented, few physicians have seen or even heard of this uncommon form of progressive osteolysis. Moreover, in none of the various reports has a satisfactory explanation of the pathogenesis of the lytic process been proposed and the etiology of the lesion is far from clear.

This communication is based upon the personal observation of two cases of this unusual disorder, one of them with autopsy which permitted a detailed study of the affected tissues, as well as a brief review of the sixteen reported cases, some of which have been painstakingly followed up. As a result of this investigation it is now possible to record the clinical characteristics of a remarkable syndrome, that of massive osteolysis, and to give a description of the pathologic changes found in one case. We have also proposed a possible explanation of the mechanism whereby the affected bones are slowly dissolved and reduced to little more than flexible fibrous bands.

CASE REPORTS

Case I. H. N., a sixteen year old white high school boy, was first admitted to the Surgical Service of the Albany Hospital on May 18, 1944, because of a deformity and pain in his right clavicle which had been fractured six months previously. The fracture was unrecognized for a week before it was immobilized with a T-splint. This was removed after six weeks, at which time there seemed to be fair approximation of the bone edges with a slight depression persisting over the mid-portion of the bone. As there was no pain or other evidence of disability, no further treatment was prescribed.

In May, 1944, while playing baseball, he felt a sudden giving-away associated with considerable pain in the region of the right clavicle and the depressed area seemed to be deeper than before. He was referred to the Albany Hospital for study.

The past and family histories were non-contributory. General examination was entirely negative except for the presence of a deep depression over the middle portion of the right clavicle. (Fig. 1.) The sternal and acromial ends of this bone were palpable but the central portion was missing. X-ray examination showed almost total absence of the right clavicle except for an indefinite small fragment at the acromial end. Moreover, much of the scapula was also missing, particularly the superior portion where only a small part of the coracoid process remained. At the base of its spine the scapula was very thin. The second rib on the right, with the exception of a 7 cm. portion of its head, was absent. The skull was normal.

Normal values were obtained in the following laboratory tests: red cells, hemoglobin, white cells, differential count, acid phosphatase, serum phosphorus, blood calcium and blood Wasser-

^{*} From the Department of Medicine and the Department of Pathology and Bacteriology of the Albany Medical College, Union University, Albany, N. Y.

[†] Present address: Director, The Public Health Research Institute of The City of New York, Inc., Foot of East 15th Street, New York 9, N. Y.

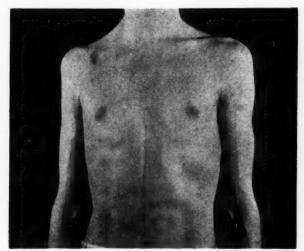


Fig. 1. Case i. Showing depression in right clavicle.

mann. The alkaline phosphatase was elevated to 8.7 Bodansky units, about twice the normal value for adults but of questionable significance in this growing sixteen year old boy.

No satisfactory diagnosis was made and the patient was discharged on May 24, 1944. Because of continued pain in the neck and upper back, and further increase in the deformity of the right shoulder girdle, the patient was admitted to the hospital again on March 9, 1945, this time for observation on the Medical Service. He did not appear ill but there was marked atrophy of the muscles of the right shoulder girdle with drooping of the shoulder forward and downward. The right clavicle was reduced to a fibrous cord beneath which could be felt the stumps of the second and third ribs projecting from the sternum. There was scoliosis of the lower cervical and upper thoracic vertebrae with convexity to the right. The head could not be completely turned to the right. There was marked weakness and limitation of movement of the right arm but the strength and motion of the forearm and hands were undiminished. The reflexes were normal except for a weaker biceps jerk on the right. The right testis was not palpable.

Skeletal x-rays revealed further destruction of the right scapula. In addition, the head and neck of the right humerus, the upper three ribs on the right side and the upper three dorsal vertebrae were now involved.

The red cells numbered 4,320,000 and the white cells 4,900 per cu. mm. The differential count was normal. Hemoglobin was 8 gm., non-protein nitrogen 31 mg., serum calcium 10.7 mg., serum phosphorus 4.3 mg., cholesterol 101 mg. and acid phosphatase 3.3 units, all per 100 ml.

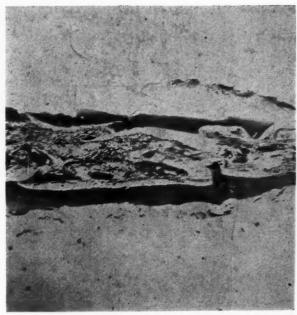


Fig. 2. Case i. Biopsy of third right rib; × 30.

of blood. Alkaline phosphatase was 8.4 Bodansky units. The urine was normal. No albumin was found on several examinations.

A modified Aschheim-Zondek test made on the urine of the patient gave a negative reaction. Sternal puncture revealed an essentially normal marrow with the exception of the presence of slight eosinophilia and a deficiency of reticulocytes. All cells were qualitatively normal when examined by the supravital method.

Biopsy of the third right rib showed marked atrophy of the bone which consisted of little more than a paper-thin cortex enclosing brownish marrow. There was no evidence of tumor. Histologically, much of the cortical and cancellous bone had disappeared and that which remained was surrounded by osteoclasts. The fibrous periosteum was thin but normal. The marrow was composed of atrophic fat with a few centers of normal though underactive hematopoiesis. Blood vessels, chiefly congested capillaries, were numerous. There was no evidence of inflammation. The etiology and nature of this extreme generalized atrophy were completely obscure. (Fig. 2.)

The patient was discharged on the twenty-second hospital day and was not seen again until August 23, 1945, when he was admitted for the last time because of increasing pain in the right shoulder, progressing generalized weakness and the onset three weeks previously of severe exertional dyspnea, anorexia and dull, non-radiating epigastric pain. There had been

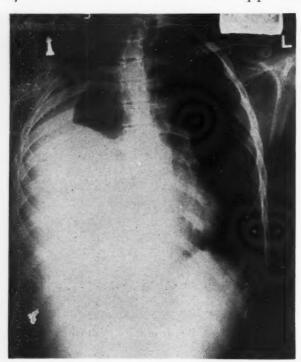


Fig. 3. Case I. X-ray of chest showing extensive osteolysis and pleural effusion.

moderate loss of weight since the last admission. The right chest now contained fluid and the heart was displaced to the left. There was marked tenderness in the epigastrium with an indefinite mass in this region. The deformity of the right shoulder girdle and arm and the scoliosis of the upper spine were more marked than they had been and atrophy and weakness of the involved muscles were present.

Roentgenograms revealed evidence of massive pleural effusion on the right with displacement of the mediastinal structures to the left (Fig. 3.) The destructive changes in the upper three ribs, the scapula, cervical vertebrae and thoracic vertebrae had increased since the previous examination.

Fluid obtained by thoracentesis was bloody but was sterile on culture. It contained 1,850,000 red blood cells and 14,000 white blood cells per cu. mm., 70 per cent of the white cells being lymphocytes. No tumor cells were found.

The red blood cells numbered 3,845,000, white cells, 7,800 per cu. mm. The differential count was normal. Hemoglobin was 13 gm., non-protein nitrogen 32 mg. and serum phosphorus 3.6 mg. per 100 ml. blood. Alkaline phosphatase was 5.3 Bodansky units. Urine examinations were negative. The calcium in urine ranged between 9 and 11 mg. per 100 ml.

No Bence-Jones protein was found on numerous examinations.

The patient's course was steadily downhill. Repeated thoracenteses performed at intervals of two to three days yielded amounts of fluid varying from 600 to 1,100 ml. The character of the fluid changed from a sanguineous to a frankly chylous type but was always sterile on culture and contained no tumor cells. Decubitus ulcers appeared over the sacrum, he became more emaciated and died 180 days after the final hospital admission, two years and five months after the fracture of his clavicle.

At necropsy, the body was thin and wasted. There was marked inflammatory edema of the tissues of the right thorax, shoulder and neck, and a depression was present in the right clavicular region. When exposed these tissues exhibited diffuse phlegmonous inflammation which extended into the anterior mediastinum. The right clavicle and the first and second right ribs were missing and the third rib was thin and flat. The right scapula was atrophied and parts of it had disappeared. There was marked flexion deformity of both knees and large decubitus ulcers were present on the back.

The right pleural space contained 2,000 ml. of milky fluid and the serous surfaces were thickened and sclerosed. The upper part of the thoracic duct was compressed and lost in the inflamed mediastinal tissues, thus leading to its obstruction. The heart was small, weighing 160 gm. and was displaced to the left. The lungs were collapsed and atelectatic, especially on the right where dense adhesions were also present. The right testis was undescended and small, and lay in the inguinal canal. The brain was congested and edematous but the cervical portion of the spinal cord was soft and hyperemic. The bodies of the cervical and upper thoracic vertebrae were soft, reddish-gray and focally cystic. The lumbar vertebrae were normal.

The most significant histopathologic changes were found in the soft tissues of the chest wall and mediastinum and in various bones, particularly the ribs and the bodies of several cervical and upper thoracic vertebrae. In the soft tissues were found evidences of extensive chronic active cellulitis, with diffuse hyperemia, edema and inflammation. Many tissues, especially fat, skeletal muscle and lymph nodes, were atrophied and diffuse interstitial fibrosis was present. Perineural inflammation and fibrosis were often so striking that many nerves were

compressed by either exudate or inflammatory scar tissue.

Sections from portions of several ribs showed atrophy of bone, increased vascularity of marrow and reduced hematopoiesis. The vertebral marrow was extremely vascular, large, blood-filled, thin-walled vessels practically replacing the normal fat tissue and causing great reduction in hematopoietic activity. The vascularity was so significant as to lead to the diagnosis of hemangiomatosis (Fig. 4), a term proposed by A. Purdy Stout in 1946 (King⁹).

Case II. I. G., a forty-four year old white man, was seen on February 11, 1953, by one of us (L. W. G.) with Dr. Charles M. Hanisch, consultant in Orthopedics to the Jamaica Medical Group of the Health Insurance Plan of New York City, who kindly placed the patient's previous record at our disposal. We are indebted to him for the privilege of recording these observations.

The patient was first seen in June, 1949, by Dr. Nathan Brody at the Flatbush Medical Group of the Health Insurance Plan in Brooklyn. His chief complaint was of right shoulder pain which had been precipitated six months previously when he reached for an object above his head, and which had continued intermittently since that time. During the last few weeks it had become more disabling and had extended to the neck. The patient denied any history of trauma.

Physically, no gross deformities or atrophies were noted. External rotation of the left arm was complete to 90 degrees; internal rotation to 70 degrees. On the right, external rotation was to 80 degrees; internal rotation to 50 degrees. Sensitive areas were present over the upper part of the right scapula and over the head of the left biceps. Neurologic examination was negative. Roentgenograms on August 16, 1949, revealed absence of the outer third of the right clavicle with some gouging of the middle third, while the inner third appeared normal. The chest was negative. The following laboratory tests were within normal limits: sedimentation time, blood calcium, blood phosphorus and alkaline phosphatase.

A tentative diagnosis of neoplasm involving the clavicle was made.

An x-ray examination on March 31, 1951, showed complete absence of the lateral half of the right clavicle and of the entire coracoid process. The upper margin of the right scapula and part of the glenoid process were destroyed

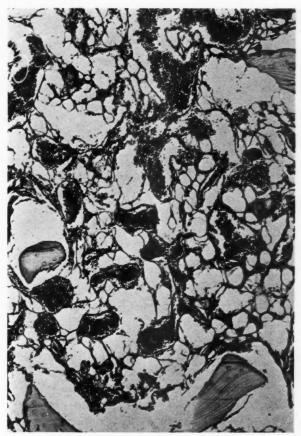


Fig. 4. Case 1. Microscopic section of vertebral marrow showing large thin-walled capillaries filled with red blood cells.

and the remaining portion of the scapula and the right humerus exhibited marked demineralization. A series of deep x-ray treatments were given.

In December, 1949, a biopsy was performed by Dr. Frederick M. Smith, at the Presbyterian Hospital, New York. A tentative diagnosis of hemangio-endothelioma was considered. However, no definite diagnosis was made. Therefore the disarticulation and intrascapular thoracic amputation, which had been under consideration, were not undertaken. In April, 1951, the patient developed an abscess in the right triceps and was treated with antibiotics. He was then admitted to the Horace Harding Hospital with fever of 104°F., where incision and drainage were performed by Dr. Hanisch. About a quart of fluid was obtained. In a month the patient had recovered and his course was uneventful until December, 1951, when there was recurrence of the swelling which was again treated with antibiotics and aspiration until it subsided.

The patient was last seen at this Clinic in August, 1952, at which time he fell from a ladder,

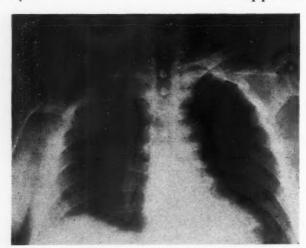


Fig. 5. Case II. Roentgenogram of chest showing partial disappearance of the right clavicle.

suffering a fracture of the right humerus with no displacement. The arm was placed in a sling. He continued to work and did not report again to the Clinic. He considered he had entirely recovered at the end of three months. An x-ray report on August 15, 1952, stated: "Part of the clavicle has been resected and osteo-arthritic changes are seen in the glenoid fossa of the scapula. Fracture of the neck of the humerus is in good position."

When seen by one of us (L. W. G.) on February 11, 1953, physical examination was entirely negative except for the right shoulder. Over the anterior aspect of this was a semicircular 8 inch scar. The middle end of the right clavicle was palpable, the outer third having entirely disappeared. Movements of the right shoulder were restricted. X-ray (Fig. 5.) showed essentially the same findings recorded on March 31, 1951.

REVIEW OF REPORTED CASES

Case I. (Jackson⁷—1838.) In 1819 an eighteen year old boy fractured his right humerus. Twice thereafter, within a short period, he fractured the bone again. After the last fracture the humerus began to disappear and after twelve years it was little more than a flexible fibrous band surrounded by well developed muscles. No further change occurred. The patient died at the age of seventy at which time the arm was removed and placed in the Warren Museum at the Harvard Medical School where it is today. No histologic examination was made.

CASE II. (Thoma, K. H. 18—1933.) This thirtysix year old housewife suffered pain and then pathologic fracture of the jaw following her third pregnancy. Roentgenograms showed progressive atrophy of the mandible which, after twenty months, was completely resorbed leaving only a flexible membrane. Biopsy showed cellular vascular fibrous tissue about the resorbed mandible with large vascular spaces about residual bone trabeculae. During the next four years other bones, notably the maxillary, palatine and sphenoid, became similarly involved and the patient died during an operation for possible parathyroid tumor.

Case III. (Dupas, Badelon and Daydé⁴— 1936.) A twelve year old boy fractured the second left metacarpal bone and five years later, the third. Roentgenograms at the time of the second fracture showed disappearance of the second metacarpal. In six months the third metacarpal had resorbed and little by little the two last metacarpals, the carpal bones and the first phalanx of the index finger also disappeared. Left brachial sympathectomy was ineffectual. At the age of twenty-two the patient had a soft, paddle-like hand with only remnants of digits. A biopsy from the hand showed fibrous tissue rich in blood vessels. When last seen in March, 1953, the patient, a letter carrier, stated that he rides his bicycle every day.

Case IV. (Simpson¹⁷—1937.) A fourteen year old girl tripped and fell in 1926, injuring the left foot which caused swelling and tenderness of the tarsus and metatarsus. After twenty-two months the third, fourth and fifth metatarsal bones, the cuneiforms and the tarsal navicular had undergone decalcification. During the following year further decalcification occurred and in 1931, five years after the original injury, no bony substance remained in the third and fourth metatarsals and only the outline of the fifth could be seen. A biopsy of the fifth metatarsal showed lack of calcium, enlarged cancellous spaces and replacement of the marrow by vascular fibrous tissue. From 1933 to 1936, "the patient walks and cycles freely and dances and plays golf without difficulty." Report of June 13, 1953, "age 39, general health good, able to work and cycle."

Case v. (Mouchet and Rouvillois¹²—1937.) In May, 1912, a twelve year old girl fell on her left hip and two months later fell again. Soon after the second fall she began to drag the left foot and then to limp, and the muscles of the left leg became atrophied. In October, 1912, and again in 1914, roentgenograms showed almost complete disappearance of the left ischiopubic bones with destruction of the acetabulum. By

1937 there had been no notable change either clinically or radiologically. No biopsy was ever made. In March, 1953, the disease had not progressed.

Case vi. (Radulesco¹⁵—1937.) In 1926 a fourteen year old boy fell and injured his wrist. Eight months later roentgenograms showed complete absence of 5 to 6 cm. of the lower radius with extensive decalcification of the epiphysis. The carpal bones were also decalcified. No biopsy was performed. Follow-up in this case was impossible.

Case VII. (Richard¹⁶—1937.) In 1916 a thirty year old man sustained an injury to his left thigh as a result of a shell explosion. Twelve years later the upper two-thirds of the left femur showed osteolysis which progressed slowly to involve the lower portion, particularly the epiphysis. No biopsy was taken.

Case VIII. (Jackman⁶—1939.) In 1932 a twenty-one year old groundsman complained of pain in the right hand after chopping wood. Tenderness was present over the middle metacarpal which was found roentgenographically to be markedly narrowed. Four years later this bone had almost completely disappeared and there was patchy erosion of the os magnum. The middle finger, because it was useless and interfered with movement of the adjacent fingers, was amputated, as was the os magnum. The pathologic changes were described as conforming to those of "fibrocystic disease." In May, 1953, this patient was well and was working. X-ray August 13, 1952, revealed only slight extension of the process.

Case IX. (Duval⁵—1939.) In 1938 a fifty-eight year old woman had cholecystectomy for cholelithiasis. Pain developed in the left leg and foot and a plaster cast was applied for a month. Twenty-one months later she was admitted to the hospital with phlebitis and edema of the left leg. Roentgenograms showed disappearance of the lower third of the tibia and the fibula, erosions of the middle third of the tibia and marked decalcification of the bones of the foot. No follow-up report.

Case x. (Mouchet and Simonin¹³—1943.) In 1939 an eight year old girl fell on a stairway and injured her left arm, causing a supracondylar fracture of the humerus and a subepiphyseal fracture of the lower end of the radius. During three weeks in a cast, when roentgenograms showed excellent reduction of both fractures, a typical Volkmann contracture de-

veloped. Three years later roentgenograms showed marked decalcification of the lower epiphysis of the humerus, the carpal bones, the proximal ends of the metacarpals and complete disappearance of the distal epiphysis of the radius with partial decalcification of the adjacent diaphysis. No biopsy was taken and no follow-up was reported.

Case xi. (Branch²—1945.) In June, 1944, a twenty year old colored soldier, otherwise well, complained of inability to raise his left arm above his head. This disability had begun one month previously after rifle drill when he noticed pain and discomfort in the left shoulder, followed later by restriction of movement. Roentgenograms showed changes in the left clavicle, scapula, humerus, ribs and thoracic vertebrae. Biopsy of an affected bone revealed the presence of abundant vascular channels, some containing numbers of red blood cells, in the medullary portion of the bone. Hematopoiesis was slight. One zone of fibrosis was found but there was no evidence of inflammation or tumor. Efforts at follow-up were unsuccessful.

Case XII. (Nicod14—1945.) In July, 1930, a fifteen year old girl suffered a spontaneous fracture of the lower third of the left ulna while exercising in a gymnasium. There was a questionable history of a skiing accident some months before. Roentgenograms showed changes in the radius at the same level. In August, 1931, the patient fell while playing tennis and fractured the radius at the site of the previously observed abnormality. At this time there was marked decalcification of the radius and the ulna was reduced to a thin fibrous band. Biopsy of the ulna showed lacunar resorption of calcium and fibrosis of the marrow with blood-filled vascular channels, lesions which were thought to be inflammatory. By 1941 resorption of the radius, ulna and carpal bones had occurred and there was marked atrophy of the metacarpals. No follow-up was reported.

Case XIII. (King⁹—1946.) In April, 1941 an eleven year old boy fell from his bicycle, injuring his left knee which became painful, swollen and discolored. By February, 1942, the swelling had involved the thigh and the leg. The patient was admitted to the hospital in April, 1942, where 1,500 ml. of sterile serosanguineous fluid were aspirated from the thigh. No fracture was present but a provisional diagnosis of hemangioma was made and mid-thigh amputation was performed. A network of blood vessels surrounding nerve

tissue was noted and the bone of the femur was very porous and broke easily. Histologically, great numbers of capillary blood vessels were found, particularly in those situations in which bony trabeculae were atrophic and widely spaced.

Two months after the operation roentgenograms showed destruction of the upper part of the femur with probable involvement of the acetabulum. By February, 1943, the stump had become swollen and discolored and by x-ray, the head of the femur and the adjacent pelvis were involved. In April a biopsy of the tissues of the left groin showed an abundance of blood vessels, chiefly of venous type, extending into extensively sclerosed soft tissues. Focal aggregations of lymphoid cells sometimes grouped about germinal centers were prominent. The lesion was interpreted as non-malignant and was designated as "hemangiomatosis." In July, 1944, roentgenograms showed progressive improvement, the punched-out areas in the affected bone apparently filling in. No follow-up report was obtained.

Case xiv. (Bickel and Broders¹—1947.) In November, 1943, a five year old girl reported that fifteen months previously she had developed a painless limp. Roentgenograms revealed a defect in the left ilium. One month later the ilium, from the sacroiliac joint to the acetabulum, had disappeared and the head of the femur had telescoped into the pelvis. Biopsy was performed on December 21, 1943. The soft tissues were edematous and oozed straw-colored fluid. Small pieces of bone and cartilage were unsatisfactory for examination but the soft tissues disclosed the presence of a lymphangioma which had infiltrated fat, fibrous tissue and skeletal muscle.

By August, 1945, the left ischium was disappearing and a year later the left innominate bone had gone and dissolution of the pedicles, facets and spinous processes of the left sides of the vertebrae had occurred. Questionable involvement of the trochanter of the right femur was also noted.

Follow-up report May 16, 1953: The patient suffers no pain but lives in a wheelchair. When she walks, she limps markedly. A second biopsy in December, 1948 was reported as hemangioma not lymphangioma.

Case xv. (Murray and Smith—1949—Cited by Coley.³) In 1928 a twenty year old white woman injured her shoulder when she tried to catch

a child who was falling from a chair. Two weeks later she lifted a cake of ice and fractured the inner third of the clavicle. By the middle of 1929 she had recovered and returned to work. In January, 1930, she felt pain on raising the arm and roentgenograms showed absence of the outer two-thirds of the clavicle. Ten months later the right scapula showed beginning resorption. In December, 1933, the clavicle had practically disappeared and the first rib was begining to resorb. In January, 1935, biopsy of the remaining part of the clavicle was performed. Peculiar changes that could not be interpreted were found. The parathyroid glands were explored and found normal. Massive serosanguineous effusion in the right chest occurred in September, 1935, and death occurred shortly thereafter. Autopsy disclosed pulmonary thrombosis and chronic endocarditis.

Case xvi. (Lièvre¹⁰—1949.) In 1949 a twenty-one year old man presented himself with a thoracic wall defect which had been present for several years. In 1942 he had been examined and found normal. In 1945 he had had severe pain in the sternal costal area for two or three days but recovered. This pain, more severe, recurred the following year but again lasted only three days. In 1947 a defect in the sternum was found during a routine employment examination. Most of the sternum had disappeared and the anterior portions of all the ribs were abnormal. The proximal ends of the clavicles could be brought into contact.

In February, 1953, the defect in the sternum had become larger and the soft tissues of the chest wall were atrophic. The pericardium and aorta appeared to be directly beneath the skin. Biopsy showed greatly altered bone but the underlying pathologic process was not clear.

Lièvre at first considered this lesion to be congenital but now believes it is perhaps similar to the disease reported by Bickel and Broders¹ (Case xiv), although he warns against concluding that the fundamental defect is a lymphangioma. Follow-up February, 1953: The lesion has progressed markedly; the patient is thin, pale and dyspneic.

COMMENTS

Atrophy of bone following disuse is a well recognized phenomenon. Generally, however, the reduction in size of the affected bone is not great, takes a long time to develop and is rarely crippling. Atrophy following injury and inflam-

AMERICAN JOURNAL OF MEDICINE

mation, of the type described by Sudek, is less common and usually produces symptoms referable to the atrophy, and may even lead to serious disability. It tends to progress fairly rapidly and results in greater degrees of atrophy than occur following disuse. However, the atrophied bone remains and may function to some degree. Osteolysis of considerable amount has been observed in rheumatoid arthritis, leprosy, malum perforans and congenital pseudarthrosis. Atrophy which actually goes on to complete disappearance of the affected bone, leaving little but bands of fibrous tissue where the bone once was, is a most uncommon condition and has been reported, as we have noted, only infrequently. It is this latter condition which developed in the case of the two patients whom we have had the opportunity of studying.

On the basis of data from our own cases and sixteen others which have been previously reported, this unusual disease occurs generally in children or young adults, only four of the patients being over twenty-one years of age. Ten were males; eight females. In fifteen cases there was a history of trauma, usually of minor character, at most associated with a fracture, sometimes of pathologic type. However, unlike Sudek's atrophy which develops soon after injury, a long interval has usually elapsed before the osteolytic process has progressed far enough to give symptoms and then the striking and unexpected roentgenographic findings have often come as a great surprise. Thus one may question whether or not trauma plays a definite etiologic role or merely complicates a disease process already present and in the end helps to bring it to light. We are of the opinion that the latter is usually the case and that the trauma is merely incidental.

This unusual lytic disease is not limited to any one bone but may involve a number of bones, notably the clavicle, scapula, ribs, sternum, humerus, radius, ulna, jaw, bones of the hands or feet, femur and pelvis. The slow disintegration affects both the cortical and cancellous elements of bone, progresses slowly and, while the process may stabilize, it usually continues until practically all osseous tissue is gone, leaving only a fibrous band, presumably the periosteum, as a residuum.

The most striking pathologic feature in all cases in which biopsy specimens have been studied is a vascular abnormality of some kind, chiefly an overgrowth of small thin-walled

vessels, a form of angiomatosis which in one instance was so striking that it suggested a malignant process. Generally, the vascular hyperplasia has been of blood vessel origin, only one case being considered at first to be lymphatic (Case xiv) but later reclassified as a hemangioma. None of the angiomatous changes, however, have been considered malignant and in nearly all cases the vessel overgrowth has not been even neoplastic. In our first case the soft tissues of the thoracic wall and the mediastinum as well as the marrow of certain cervicodorsal vertebrae were acutely inflamed, yet in our opinion this inflammation represented a complication of the underlying pathologic defect, though it may have contributed indirectly to the lytic process.

What part, if any, do the angiomatous changes play in causing the massive osteolytic changes found in these cases? We believe they play an important role although the mechanism by which bone dissolution is brought about is not altogether clear. It may well be that arterial blood is present in excessive amounts since the angiomatosis is generally of thin-walled capillary type. This form of active hyperemia might well be responsible for a disturbance in the balance of osteoblast-osteoclast activity so that there is an excess of bone destruction over bone formation. The result after a prolonged interval would be gradual resorption and lysis of bone. This concept is in harmony with the generally accepted thesis that active or arterial hyperemia may lead to destruction of bone while passive congestion favors bone formation.

An inflammatory process is another type of lesion that might affect bone growth indirectly. Hence an extensive phlegmonous inflammatory process such as was found at autopsy in our first case, as well as the secondary diffuse fibrosis that resulted from it, may have surrounded and compressed many nerves and also led to atrophy of many tissues other than bone. Trophic disturbances following nerve injury from any cause are well known and in this case the nerve lesions may have supplemented the angiomatosis in causing such extensive osteolysis. Such trophic changes, however, could be considered of only minor significance since widespread permanent injury of peripheral nerves ordinarily does not result in bone changes such as we have reported.

This unusual disease of bone progresses slowly and may cease to advance after a period of years. Only in our first case did the process inexorably lead to the patient's death and in only two of the other cases (II and xv) did the patients die, the bony lesions presumably playing no part in causing their deaths.

SUMMARY

1. Two cases of an unusual form of massive osteolysis, one with a report of autopsy findings, are described and sixteen similar cases from the medical literature have been briefly reviewed.

2. This remarkable disease affects chiefly children or young adults; males and females about equally.

3. Trauma, usually slight, is a common though probably only an incidental initial complaint.

4. Angiomatosis, usually hemangiomatosis, has been found in the affected bones or in the surrounding soft tissues in a significant number of cases to make it a possible etiologic factor by causing a disturbance in the balance of osteo-blast-osteoclast activity.

5. Diffuse inflammation of the soft tissues about the affected bones may play an indirect role in causing bone atrophy by irritation or compression of peripheral nerves thus leading to trophic disturbances not only in bone but in other tissues as well.

REFERENCES

- BICKEL, W. H. and BRODERS, A. C. Primary lymphangioma of the ilium. J. Bone & Joint Surg., 45: 517, 1947.
- Branch, H. E. Acute spontaneous absorption of bone. Report of a case involving a clavicle and a scapula. J. Bone & Joint Surg., 27: 706, 1945.
- 3. Coley, B. L. Neoplasms of Bone—Spontaneous Absorption of Bone, (Phantom Bone Disappearing Bone), pp. 688-698. New York, 1949. Paul B. Hoeber, Inc.

- 4. Dupas, J., Badelon, P. and Daydé, G. Aspects radiologiques d'une ostéolyse essentielle progressive de la main gauche. J. de radiol. et d'électrol., 20: 383, 1936. Sur un cas d'ostéolyse progressive de la main gauche d'origine indéterminée. Rev. d'orthop., 23: 333, 1936. A propos d'un cas d'ostéolyse essentielle progressive de la main gauche. J. de radiol. et d'électrol., 23: 212, 1939.
- Duval, P. Présentation de radiographes. Mém. Acad. de chir., 65: 1110, 1939.
- JACKMAN, W. A. A case of spontaneous absorption of bone. Brit. J. Surg., 26: 944, 1939.
- Jackson, J. V. S. Absorption of the humerus after fracture. Boston M. & S. J., 10: 368, 1838.
- 8. Jacob, M. See Mouchet, A. and Rouvillois, H.¹²
- King, D. J. A case resembling hemangiomatosis of the lower extremity. J. Bone & Joint Surg., 44: 623, 1946.
- LIÈVRE, J. A. Lacune de la paroi thoracique. Rév. du Rhum., 16: 286, 1949. (Same case reported by MIALARET, M. J. Resorption spontanée de la paroi thoracique. Mém. Acad. de chir., 79: 212, 1953.)
- 11. MIALARET, M. J. See LIÈVRE, J. A.10
- 12. MOUCHET, A. and ROUVILLOIS, H. Ostéolyse du bassin d'origine indéterminée. Mém. Acad. de chir., 63: 277, 1937. (Case originally reported by JACOB. Malformation peut-être congénitale du bassin s'étant manifesté pour la première fois au moment de la puberté sous les apparences d'une coxalgie. Communication à la Société Nationale de Chir., 1913.)
- MOUCHET, A. and SIMONIN, L. Ostéolyse du cubitus et syndrome du Volkmann. Rev. d'orthop., 29: 22, 1943.
- 14. Nicop, L. Ostéolyse. Helvet. chir. acta, 12: 331, 1945.
- 15. RADULESCO, A. D. Un cas curieux d'ostéolyse complète de l'extremité inférieure d'une diaphyse radiale. *J. de radiol. et d'électrol.*, 21: 304, 1937.
- RICHARD, A. Ostéolyse étendue du fémur gauche. Mém. Acad. de chir., 63: 352, 1937.
- 17. Simpson, S. An unusual case of post-traumatic decalcification of the bones of the foot. J. Bone & Joint Surg., 19: 223, 1937.
- THOMA, K. H. A case of progressive atrophy of the facial bones with complete atrophy of the mandible. J. Bone & Joint Surg., 15: 494, 1933.

Respiratory Recovery Rates after Poliomyelitis*

John F. Marchand, M.D. and Aaron T. Marcum, M.D.

New York, New York

EAKNESS or loss of the muscular movements of respiration after poliomyelitis is regularly associated with extensive paralysis of the trunk and extremities. Mental acuity is spared. The practical salvage prospects for such a suddenly disabled patient depend therefore on suitably timed management directed to control of medical complications, provision of adaptive equipment, new motivations, a gradual transition to altered use and compensatory hypertrophy of remnants of the primary or accessory muscles of respiration along with other muscles. A makeshift provision for perfunctory custodial care becomes an extravagant, unrewarding expense in the absence of a treatment schedule meeting these needs.

A five-year increase in the paralytic poliomyelitis attack rate, more effective medical care at the acute stage, and an advance in methods for mechanical artificial respiration have been followed by the recent survival of over 1,000 respirator-bound young persons in the United States, a number grossly overtaxing available facilities for needed treatment. Although life expectancy remains long in the physical sense, the medical corrective measures required can be effective if timed to minimize deterioration and the inevitable expense of life-long care. When helped promptly by control of medical complications and by adaptive measures, those young paralytics strive for a phenomenal degree of independence and resumption of a productive life. A comparison of the respiratory recovery rates of twenty recently convalescent poliomyelitis patients treated under emergency conditions highlights one aspect of this comprehensive care problem.

Survivors of a 1952 poliomyelitis epidemic

included fourteen quadriplegic respiratory cripples remaining in an improvised area of the Louisville General Hospital on March 1, 1953. During eight following months of medical management under the direction of the authors six more recent poliomyelitis victims with impaired respiratory function were admitted or transferred to the same area on an emergency basis. Unacceptable at general rehabilitation centers throughout the country, none of these extensively paralyzed children and young adults could be offered placement at that time for suitable convalescent treatment. Mechanical respiratory equipment was available, however, to sustain vital function pending such placement.† The sixteen cases dating from 1952 and four from 1953 illustrate varying rates and degrees of respiratory recovery and some influences on the rate of recovery.

Although the most rapid improvement followed early regeneration of the diaphragm, respiratory recovery to a limited extent also occurred in a year or more following recovery of only a portion of the diaphragm, or through hypertrophy and new habituation of remnants of voluntary accessory respiratory muscles. For example combinations of the pretracheal muscles, the platysma, one or both sternomastoid

† The mechanical respiratory equipment supplied by the National Foundation included: tank respirators and rocking beds manufactured by the J. H. Emerson Co., Cambridge, Mass.; a tank respirator made by the Warren E. Collins Co., Cambridge, Mass.; chest cuirass respirators by the J. J. Monaghan Co., Denver, Colo.; and chest-abdomen cuirass respirators by Conitech, Ltd., New York, N. Y. The patients were fitted with wheel-chairs made by the Everest and Jennings Co., Los Angeles, Calif. A description of such equipment is available from the suppliers.

^{*} From a provisional Center for Poliomyelitis of the University of Louisville, Louisville, Ky. Aided by a grant from the National Foundation for Infantile Paralysis.

muscles, and remnants of rib muscles became capable of raising the rib cage for inspiration, while enlarging remnants of muscle in the abdominal wall aided expiration. Self-taught frog breathing, glossopharyngeal breathing, was of supplementary value to one patient in this

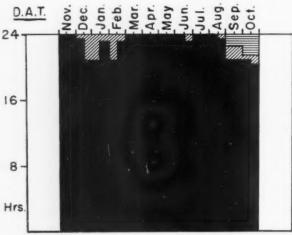


Fig. 1. Case I. Solid black indicates a summation of the proportion of the day spent in a tank respirator, diagonal hatching the proportion in a cuirass respirator and horizontal hatching the proportion on a rocking bed. Use of the rocking bed increased after October, 1953, when this record ended.

group. In extreme cases muscles of the trunk and extremities remained valueless but good use was made of improved mechanical aids. Of five respiratory paralytics observed by the authors at the acute stage four made a rapid recovery; the fifth remained extensively paralyzed but transferred to a rocking bed and chest-abdomen cuirass respirator schedule in two months.

These respiratory cripples illustrate several of the care problems which follow paralytic poliomyelitis. For brevity, however, the details of paralysis and joint fixation are summarized rather than itemized and routine laboratory reports or treatments are omitted unless of special interest. All the patients of the series developed stiff joints and atrophic muscle contractures inadequately managed by bracing or physical therapy and unaided by occupational therapy. In the months prior to March, 1953, they were subjected under varying medical direction to successive forced trials of insufficient mechanical aid or unassisted respiration.

Cases I and II were the most extensively and irreversibly paralyzed of the group. Each ultimately learned to transfer at will from the tank

*Dail, C. W. Glossopharyngeal breathing by paralyzed patients. *California Med.*, 75: 217, 1951.

respirator to less complete but otherwise more satisfactory respiratory aids such as the chestabdomen cuirass respirator and the rocking bed.

CASE I. Skeletal and respiratory paralysis; anorexia and undernutrition; paralytic ileus; fecal impactions; thrombophlebitis; hypertension; acne. D. A. T., a schoolboy seventeen years of age, had a dry cough for two weeks, constipation, fever and a stiff neck one week after a brother age six became ill and partially paralyzed. On October 26, 1952, he entered the hospital with a rectal temperature of 104°F., a pulse rate of 110 beats per minute, a respiratory rate of 20 per minute and an arterial blood pressure of 130 mm. Hg systolic and 60 diastolic. A day later weakness and dyspnea made necessary a chest respirator, then a tank respirator and then tracheotomy because of inability to swallow. The skeletal muscles from the chin down became paralyzed and for a week the bladder ceased to empty without the aid of a catheter. In the following months he took nourishment poorly, remained emaciated, had frequent fecal impactions and had two brief attacks of paralytic ileus. There was thrombophlebitis of the left leg for two weeks in March, 1953. Throughout March, April and May an arterial hypertension of 140 to 160 mm. Hg and 110 to 125 diastolic was followed by a decline in October to 130 systolic and 90 diastolic. The urine specimens contained only a few casts and erythrocytes. In September and October the nutrition improved, although motor paralysis below the face level remained virtually complete.

Respiratory schedule: In December, 1952, and thereafter there were unsuccessful attempts at use of a chest-abdomen respirator for up to two hours. Because of emaciation it was difficult to fit such a cuirass. After the nutrition improved, however, he learned to divide up to five hours a day between time on a rocking bed and time in a chest-abdomen cuirass respirator. The vital capacity* of this 5 foot, 6½ inch boy never exceeded the negligible value of 25 ml. (Fig. 1.)

CASE II. Skeletal and respiratory paralysis; pulmonary hemorrhages, atelactasis; anxiety and depression; acne, hirsutism, amenorrhea; fecal impactions; decubitus ulcer of neck; undernutrition; pyelonephritis, renal calculi. B. A., a fourteen year old school-

AMERICAN JOURNAL OF MEDICINE

^{*}The vital capacity was measured by a Sanborn Metabular basal metabolism apparatus used as a spirometer. Except as noted, the vital capacity was measured while the patient was in a supine position.

girl, had coryza followed by a cough for three weeks. On September 23, 1952, she felt chilly, the neck was stiff and painful, and the left arm weak. After a sleepless night she entered the hospital with a fever of 101°F., a respiratory rate of 48 per minute and obvious respiratory distress. Accessory muscles of respiration about the neck and nostrils were active, the breathing shallow and mechanical respiratory aid became necessary. Cough, gag and swallowing movements were inadequate and both arms were weak. There was a blotchy erythema over the trunk. The urine was concentrated and acid and gave an albumin reaction graded 2 plus by the heat and acetic acid test. On the ninth day in the hospital tracheotomy was performed. Nursing care of this depressed, agitated and demanding patient remained difficult. From the third week there were multiple episodes of pulmonary atelectasis and infiltration treated by frequent bronchoscopies through the tracheotomy. There were two unexplained but massive pulmonary hemorrhages. From the third month there were renal calculi associated with blood and gravel in the urine. From the fifth month these concretions assumed a stag horn configuration, while skeletal structures appeared more than usually translucent by radiography. For six months from November, 1952, there was a posterior ulcer of the neck under the respirator collar. There was a chronic urinary infection by gramnegative bacilli, but no hypertension. The paralyzed arms and legs became hirsute and there was acne vulgaris of the face which gradually improved. After ten months the quadriplegia remained but enough abdominal muscle had returned to make possible a weak cough justifying removal of the tracheotomy tube. Menses ceased following onset of the paralysis.

Respiratory schedule: On the first day in the hospital the twenty-four-hour trial of a cuirass chest respirator was unsuccessful and a tank respirator was required. After a month there was an unsuccessful trial of unassisted respiration for ten minutes followed on two successive days by similar trials for three minutes to the stage of asphyxia. These forced efforts were interrupted by pulmonary complications but there were occasional subsequent attempts at unassisted breathing up to nine minutes at a time for the first three months. Trials of a cuirass chest respirator for up to twelve and even twenty-four hours on a forced basis were ultimately limited by exhaustion and collapse. A trial of

graded intervals of unassisted respiration, from five to forty minutes, also led to exhaustion and resumption of full time use of the tank respirator. From the sixth to eighth month, on a less abruptly graded schedule, she learned to breathe unaided without fatigue for graduated intervals

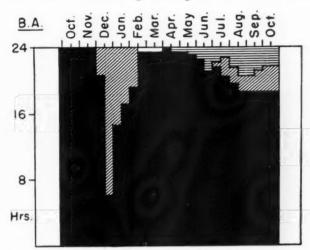


Fig. 2. Case II. Attempts at a rapid transfer from the tank respirator to a chest cuirass respirator in December, 1952, the third month of disability, were followed by a relapse. Brief trials of unassisted respiration are shown by a margin of white space in February and March, 1953. A gradual increase in the use of a cuirass respirator and a rocking bed was tolerated over the final six months. See Figure 1 for key.

which reached fifteen minutes, and to use of a rocking bed and cuirass chest-abdomen respirator alternately up to four hours a day. The vital capacity of this 60 pound, 5 feet, $4\frac{1}{2}$ inch girl did not exceed 100 ml. (Fig. 2.)

Cases III to XI are an extensively paralyzed group who made fractional recoveries by regeneration of a minor proportion of diaphragmatic function, and by enlargement of remnants of accessory respiratory muscles.

Case III. Skeletal and respiratory paralysis with partial early recovery; hypertension; bronchopneumonia; pyelonephritis. W. A., a thirty-one year old farmer, had nausea and a headache followed in a day by weakness of both legs. On June 3, 1953, in respiratory failure, he was incorrectly fitted with an inadequate portable type chest respirator for transportation 130 miles by ambulance. Cyanotic and unresponsive on arrival at the hospital, he required a tank respirator at once, and recovered consciousness but remained apathetic and cyanotic. The rectal temperature was 102°F. Tracheotomy was necessary, and pink mucus was aspirated from the airway. For the following week repetitious aspiration by

tracheal catheter was necessary for removal of mucus, purulent matter and firm bronchial plugs with a fetid odor. The initial arterial blood pressures of 180 mm. Hg systolic and 120 diastolic declined to normal after four days. There was pyuria and a mixed urinary infection

dry and irregularly erythematous. A tank respirator was required but no tracheotomy. During three months of tube feeding and forced trials of a chest cuirass respirator this patient remained emaciated but developed arterial hypertension. At 5 P.M. on December 29th, after

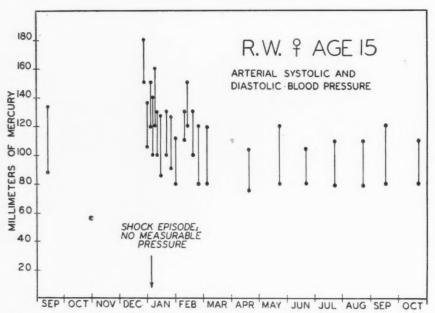


Fig. 3. Case IV. In the third month following the onset of paralysis there was a transient but critical hypertensive episode with papilledema, delirium and convulsions.

following the catheterization. To drain the bronchi, the foot of the respirator was frequently elevated. This patient, 6 feet, 3 inches tall, did not fit the standard tank respirator; the superior aspects of both shoulders became temporarily ulcerated by pressure. Within two weeks on postural drainage the cyanosis disappeared and he was transferred completely to a schedule of alternation between a cuirass chest-abdomen respirator and a rocking bed, although he occasionally felt dyspneic for an hour or two. While there was little recovery of use of the extremities, the vital capacity increased from 15 to 300 ml. in six months.

CASE IV. Skeletal and respiratory muscle paralysis; hypertension, delirium, convulsions; amenorrhea; undernutrition; pyelonephritis. R. W., a fifteen year old school girl, had a headache, backache, stiff neck, and weakness of the arms and legs for three days preceding her September 13, 1952, hospital admission because of respiratory distress. The rectal temperature reached 102°F., the pulse rate 120 beats per minute, the respiratory rate 30 per minute, the arterial blood pressure 130 mm. Hg systolic and 80 diastolic; the skin was hot,

a history of recurrent unilateral headaches, there was a large visual scotoma followed in five minutes by a tonic-clonic bilateral contraction of the face muscles, downward deviation of both eyes for one and a half minutes, and a headache. After three such seizures fifteen minutes apart the patient appeared cyanotic and the alae nasae flared. The arterial pressure, noted a day later, had become 180 mm. Hg systolic, 150 diastolic, and an ophthalmologist noted choked optic discs. Oral doses of 25 or 50 mg. of apresoline® every six hours were followed by a transient reduction in the arterial tension, but a trial of intravenous magnesium sulfate had no such effect. A prompt, near-fatal vascular collapse to a shock state halted the intravenous trial of a sympathetic blocking agent, arfonad,® on January 3, 1953. One day later the patient was confused and screaming with hallucinations of small animals. After another day the mental confusion diminished and the optic fundi were interpreted as nearly normal, although the arterial tension was still 160 mm. Hg systolic and 140 diastolic. Dilantin® and phenobarbital were administered thereafter, by way of the

AMERICAN JOURNAL OF MEDICINE

stomach tube. In March, after these anticonvulsant drugs had been stopped for a month, another seizure occurred and both were resumed despite the development of drowsiness and hypertrophic gingivitis. In the same month, following discontinuation of forced respiratory weaning efforts, the appetite returned and tube feeding became unnecessary. Acne vulgaris of the face improved after ultraviolet light therapy. Well defined hirsutism remained of the face and of the stiffened, wasted and useless extremities. There was an intractable urinary infection by mixed organisms but no evidence of renal calculi. The arterial hypertension gradually reverted to normal, as shown in Figure 3. Amenorrhea accompanied this paralysis.

Respiratory schedule: Following a trial for three days, the chest cuirass respirator proved inadequate and a tank respirator became necessary. In October, November, and December, as the unassisted breathing capacity increased progressively from one to one and a half, then six and finally twenty minutes a day, she was pushed rapidly to full time use of a chest cuirass respirator for an interval preceding the collapse and hypertensive episode of the end of December. A hasty transfer from the tank respirator and rocking bed began again in January and February, 1953. From March, 1953, to avoid further collapse and relieve the tube-feeding problem, the rate of withdrawal of mechanical assistance was sharply reduced to conform with the patient's own estimate of tolerance and fatigue. In April, although she continued to use the tank respirator at night, ability to breathe unassisted had returned to the extent of five minutes twice a day, and the remainder of the day was divided between time in a chest cuirass respirator and time on a rocking bed. In the next six months there was a gradual transfer to full time reliance on the chest respirator and rocking bed, with intervals of twenty minutes unassisted three or four times a day, and use of the chest cuirass at night in place of the tank respirator. In August, when she began using a wheelchair for half-hour intervals while wearing the cuirass, the fluoroscope revealed a distinct movement of the right diaphragm but only a flicker of the left. Although there was only enough active muscle in the extremities to move the fingers slightly, enough abdominal muscle returned to allow a cough and justify closure of the tracheotomy. Whether in the supine or sitting position she learned to elevate the chest by contraction of a hypertrophic right platysma, an enlarged left sternomastoid and the pretracheal muscles. During such respiratory movement while the patient was supine, the weight of the head balanced the force applied by these muscles to the thorax, but did not prevent the development of

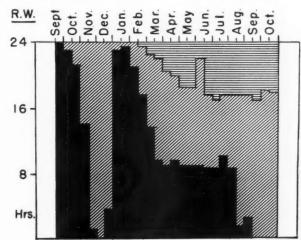
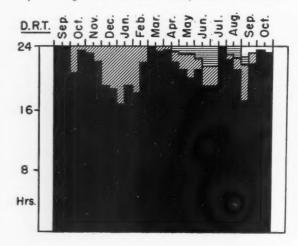


Fig. 4. Case IV. The rapid transfer from a tank to a cuirass respirator in 1952 was followed by relapse and the hypertensive interval. A gradual transfer to a cuirass respirator and rocking bed schedule was relatively uneventful in 1953, although the vital capacity did not improve. See Figure 1 for key.

torticollis. This 63 pound, 5 foot, 1 inch girl had a slowly declining vital capacity of the order of 300 ml. in the last half of the first year of her disability. (Fig. 4.)

CASE V. Quadriplegia with respiratory paralysis; hypertension; Raynaud's disease; atelectasis; pyelonephritis, renal calculi and nephrolithotomies. D. R. T., a seventeen year old store clerk, had a sore throat and cough on August 20, 1952, followed for ten days by constipation, myalgia, headache, weakness and pain in the legs. He was dyspneic and cyanotic when rushed to the hospital on the eleventh day, appeared critically ill and was unable to speak. He could grasp weakly with each hand and move the left forearm, but later lost these movements. He was placed in a tank respirator at once, treated with oxygen and parenteral fluids, catheterized periodically and had a tracheotomy on the fourth day. After two weeks in the hospital he had a refractory mixed urinary infection which persisted thereafter, an intermittent arterial hypertension amounting to 130 mm. Hg systolic and 90 diastolic, and an icy cold dripping-wet condition of the hands and feet. Right upper lobe pulmonary atelectasis in February, 1953, was relieved following bronchoscopy. In the same month small calculi were

first seen in both kidneys. Because of febrile obstructive episodes a left ureterolithotomy was performed in July, and a left nephrolithotomy in September, each of these procedures followed by a gush of purulent urine from the obstructed kidney. The joints became stiff, and both arms



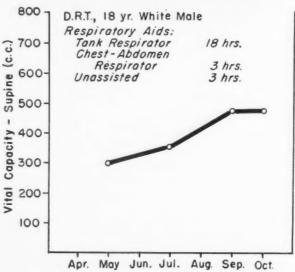


Fig. 5. Case v. Six months of continuing effort to transfer the patient from a tank to a cuirass respirator were followed by relapse. Subsequent gradual transfer to a chest-abdomen cuirass respirator and to a rocking bed was temporarily interrupted twice, in June and September, 1953, by surgery for impacted renal calculi. An expanding vital capacity in the final six months permitted increasing intervals of unassisted respiration a year after onset of the paralysis.

and legs remained paralyzed. He had mild acne but no unusual hirsutism. The cold and wet condition of the hands and feet was most striking at times of stress but gradually improved.

Respiratory schedule: Ten days after the original emergency placement in a tank respirator he made efforts at unassisted respiration for a minute at a time, but no respiratory movements

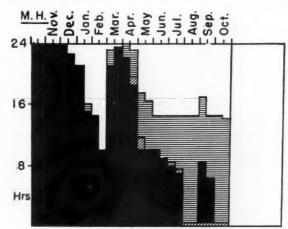
could be seen. After the first month there were forced trials of a rocking bed up to twenty-five minutes and of a chest cuirass respirator for thirteen hours for two days, followed by a relapse to physical exhaustion and a tolerance reduction to only half an hour a day in the chest cuirass respirator. Five subsequent months of effort at forced transfer to inadequate respiratory aid again led to exhaustion and continuous dependency on the tank respirator at the end of February, 1953. For four months from March to the ureterolithotomy in July the patient began frequent short graduated exercises at unassisted time, the chest-abdomen cuirass respirator and the rocking bed well within the limits of subjective tolerance and fatigue. He was taught to try exercising neck muscles frequently. During this interval hypertrophy of the sternomastoid muscle on the right and of the platysma bilaterally became evident, and he learned to use these muscles against the weight of the head to raise the thorax for inspiration in either supine or semi-reclining positions. From two minutes of unassisted time in April he gradually progressed, despite the interruption for surgery in July, to a greater degree of independence. In May he spent two to five hours in the chest-abdomen cuirass respirator, one hour daily on the rocking bed and practiced two minutes unassisted every hour. In June and half of July he alternated two and a half hour intervals in the cuirass and on the rocking bed with seven to ten minutes of unassisted breathing. After the ureterolithotomy of July 15th he was kept in the tank respirator continuously for three weeks, but thereafter rapidly returned to the former schedule and increased the unassisted intervals to thirty minutes. In September, following the second lithotomy, he resumed almost full time use of the tank respirator for three weeks but continued to practice unassisted for half an hour to one hour a day in divided intervals. This 6 foot, 4 inch boy became well nourished in the final six months of his first year of disability. He increased his vital capacity over the same interval from 300 in May to 480 ml. in November, and learned to breathe three hours a day unassisted. (Fig. 5.)

Case VI. Respiratory paralysis with quadriplegia; hypertension; undernutrition; decubitus ulcer of neck. M. H., a six year old schoolboy, had complaints of headache, vomiting, fever, pain in both legs and weakness of the left leg for a day or more before his October 1, 1952, admission to a hospital at Glasgow, Kentucky. The rectal

AMERICAN JOURNAL OF MEDICINE

temperature was 106°F., the pulse rate 110 beats per minute, the arterial blood pressure 110 mm. Hg systolic and 70 diastolic, and the respiration apparently labored at 30 per minute. The neck was stiff and the muscles of the extremities were tender. He became unable to move the arms or legs, or to empty the bladder. When the respiratory muscles failed, he was placed in a tank respirator but had no tracheotomy. In November there was bilateral bronchopneumonia. In December and January, 1953, he spent increasing periods up to three hours a day of breathing without mechanical aid until he was transferred to the hospital in Louisville on January 13th. On the date of this move he appeared poorly nourished and chronically ill, and had a large respirator-collar pressure ulcer of the back of the neck. The pulse rate was 110 beats per minute, the respiratory rate 24 per minute and the arterial blood pressure 180 mm. Hg systolic and 120 diastolic. Voluntary anterior neck muscles were active as each breath was taken. The arms, legs and trunk were completely paralyzed, and the joints limited in range. After reaching 200 mm. Hg systolic and 120 diastolic, the arterial blood pressures gradually receded over three months to 120 systolic and 70 diastolic in March. The ulcer of the neck healed in May after the patient emerged from the tank respirator; the nutrition improved and he learned to sit passively in a wheelchair while supported by a body corset. This preadolescent child had no dermatosis or unusual growth of hair. He became cheerful and appeared to accept his disability with equanimity.

Respiratory schedule: After six weeks of continuous use of a tank respirator the patient was taken out on a schedule of unassisted time which increased rapidly in a month to three hours a day despite a generally poor condition and hypertension. This precipitous weaning schedule, carried through January and February of 1953 to fifteen hours a day of unassisted time, ended with a relapse to almost full time dependency on the tank respirator at the end of February. In April he was placed on a gradual progression, adjusted each day within limits of subjective fatigue, to the rocking bed and unassisted time. The chest cuirass respirator was used as an exercise half an hour a day in the hope of maintaining or restoring some flexibility of the chest wall. In May, June, and July he slept in the tank respirator at night and divided the day intermittently between rocking bed time and unassisted time. The ulcer of the neck healed. In July, after he had been spending eight hours a day unassisted, he elected prematurely to switch from the respirator to the rocking bed for sleep at night. Although he did sleep through, he rested less well on the rocking



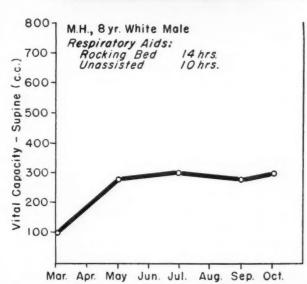
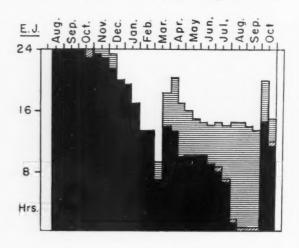


Fig. 6. Case vi. A relapse in the sixth month followed efforts at a quick changeover to unassisted respiration. Although the vital capacity increased to a plateau of only 300 ml. in the final months of observation in 1953, brief daily exercise in a cuirass respirator and a gradual progressive transfer to the rocking bed were undertaken. A return to the tank respirator for sleep was encouraged to assure adequate rest during this transition.

bed at first; and in August and September he frequently returned to the tank respirator for better sleep. In October and November he alternated between rocking and unassisted time by three-hour shifts and slept all night on the rocking bed. Respiration was by anterior neck muscles, notably the enlarging sternomastoids, and by right diaphragmatic action first noted by fluoroscopy in May. In October there was a

positive Litten sign, a moving shadow of diaphragmatic action on the right lower thorax. For inspiration in the supine position, the action of the anterior neck muscles was balanced by the weight of the head. He did not learn to balance the head well or breathe well sitting, since each



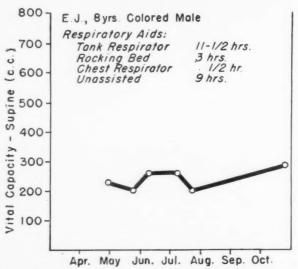


Fig. 7 Case vii. Attempts to break dependency on the tank respirator in four months following the onset of the paralysis were followed by signs of exhaustion and a need for prolonged respiratory aid. A more gradual transfer to the rocking bed and unassisted time was also interrupted by fatigue until use of the tank respirator at night was resumed. There was little increase in the vital capacity.

respiratory effort pulled the head forward. Well nourished at 48 pounds, this 4 feet, 4 inches tall boy had a vital capacity which increased from 100 to 300 ml. in the last eight months of his first year of disability. (Fig. 6.)

CASE VII. Respiratory paralysis with quadriplegia; atelectasis with pneumonia; breathing aided by glossopharyngeal movements. For three days a Negro

schoolboy, E. J., age seven, had pain in the head and neck, nausea, constipation and finally paralysis of the right arm and leg. At the hospital on August 20, 1952, he had a rectal temperature of 103°F., a pulse rate of 130 beats per minute, a respiratory rate of 44 per minute, an arterial blood pressure of 96 mm. Hg systolic and 60 diastolic. The neck was stiff. The chest did not expand with inspiration, and the left arm, right leg, back and abdominal muscles were weak. He required mechanical respiratory aid within a day and became paralyzed in all four extremities after six febrile days. In the third month there was right upper lobe atelectasis with pneumonia and fever. There was an unusually painful limitation of motion of the skeletal joints, particularly the elbows and shoulders, associated with striking radiographic evidence of demineralization of the bone adjacent to these joints, but no hypertension, acne, hirsutism or renal calcification. He recovered no active muscle power in the trunk or extremities, but remained mentally alert and learned to sit in a wheelchair when supported by a corset. Enough neck muscle function returned to allow him to balance the head.

Respiratory schedule: Because of a neuromuscular respiratory failure on the second day in the hospital this boy was tried for six hours in a chest cuirass respirator and then placed in a tank respirator. He had no tracheotomy. After a week he began brief efforts at unassisted respiration amounting to six minutes at a time after the second month and up to five hours a day at the end of December. Through January and February, 1953, he was carried on a precipitous schedule of transfer from the tank respirator to unassisted time until March, when he had remained unassisted for nine to fifteen hours a day but became tired and had to be put back on mechanical respiratory aid for a larger proportion of the time. Each breath still required obvious voluntary effort by accessory respiratory muscles, particularly the sternomastoids. Sucking movements of the tongue and pharynx were also used at will to supplement the volume of air inspired (frog or glossopharyngeal breathing). In April diaphragmatic action was easily visible on the right but only a slight flicker on the left side as observed by fluoroscopy; no Litten sign was noted until six months later. Over the final six months of the first year of disability there was a graded progression to nine or ten hours a day of unassisted time, and a

AMERICAN JOURNAL OF MEDICINE

gradual substitution of the rocking bed for the tank respirator. A month after the transfer from the rocking bed to the tank respirator for sleep at night he became subjectively fatigued and resumed use of the tank respirator for sleep, although he continued to use the rocking bed and to spend ten hours unassisted during the day. The chest cuirass respirator was used for half-hour intervals daily as an exercise. In the final months of the first year of disability the vital capacity measurements for this 33 pound, 4 feet, 3 inches tall boy were between 200 and 300 ml. (Fig. 7.)

CASE VIII. Respiratory paralysis and quadriplegia; recurrent atelectasis and pneumonitis; decubitus ulcer of neck; joint deformity; pyelonephritis; undernutrition. C. H., a four year old boy, had fever and a sore throat, anorexia, irritability, lethargy, a stiff neck, weakness of both legs, followed by respiratory distress in the ten days preceding a hospital admission on August 21, 1952. At the time of arrival on the ward he was unresponsive and cyanotic. The rectal temperature was 101°F., the pulse rate 100 beats per minute and the respiratory rate 54 per minute. The respiration was rapid and shallow; only the abdomen moved. The extremities and trunk did not move, the tendon jerk reflexes were absent, and the Brudzinski and Kernig signs were positive. After an eight-hour delay and a three hour trial in a chest cuirass respirator he was placed in a tank respirator where he became less cyanotic. He had no tracheotomy, although suction of secretions from the pharynx was necessary. Although he was able to take food and fluid by mouth, the nutrition remained poor and the general condition deteriorated as an ulcer of the decubitus type developed on the back of the neck under the respirator collar. Limited use of the fingers and of the toes of one foot returned. On October 10th, when transferred to another hospital, he weighed 29 pounds but continued to lose ground through a series of complications including a febrile transfusion reaction, a mixed urinary infection and recurrent pneumonitis requiring frequent bronchoscopy through a tracheotomy carried out in February. Throughout February and March he had pulmonary hemorrhages, recurrent intervals of cyanosis even with continuous oxygen therapy, and was thought to be in exodus. However, the pulmonary and urinary infections gradually improved under treatment, and the chest films resumed a normal appearance except as they reflected a general appearance of bony decalcification.

On September 9th, when readmitted to the general city hospital for respiratory re-education, he was undernourished but mentally alert. He had a marked flexion deformity of the right

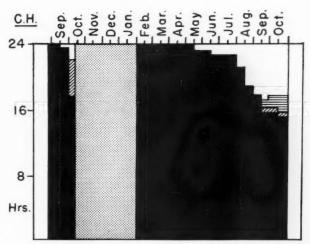
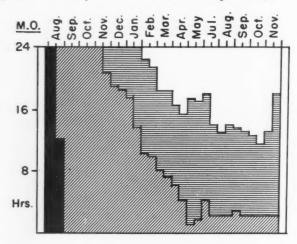


Fig. 8. Case VIII. Early in convalescence daily efforts to break the dependency on a tank respirator were interrupted by pulmonary atelectasis and infection and a temporary transfer to another hospital, the stippled area of the graph being an interval during which no respiratory record was kept. A partial changeover to lesser mechanical aids and unassisted time is shown over the last six months of observation. See Figure 1 for key.

foot, and such a degree of stiffness of the joints that he could not be placed in a sitting position.

Respiratory schedule: In the month after entering a tank respirator this child learned to breathe unassisted first long enough for a linen change, then for as long as forty-five minutes at a time if someone remained nearby. Although the action required much voluntary effort by anterior neck muscles, he was even pushed to four-hour intervals of unassisted respiration in the first week of October. In the four-month gap during which no respiratory records were kept at the hospital to which he had been transferred, the pulmonary complications noted made necessary the uninterrupted use of a tank respirator most of the time, and constant oxygen therapy was also provided. The recovery from May onward permitted a graduated transition to unassisted time, over six months, up to nine hours a day. When readmitted in September to the ward where other children with respiratory disability were present, he recovered confidence in cuirass respirators and rocking beds and learned to use each at will. This child had only a vestige of the sternomastoid muscles, but active

pretracheal muscles which helped move the thorax for inspiration. The paralyzed right diaphragm remained elevated, but movement of the left diaphragm was demonstrable by fluoroscopy. Although the weight of this 4 feet, $\frac{1}{2}$ inch tall boy had declined to 23 pounds, his



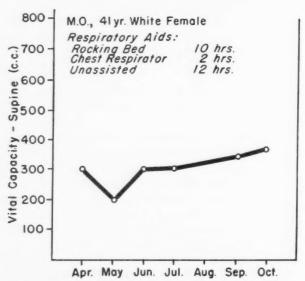


Fig. 9. Case IX. Enough functional respiratory muscle was spared to permit an early transfer from the tank respirator to lesser aids. Unassisted time became allowable after the first six months. The vital capacity remained too low for easy respiration.

vital capacity of 300 ml. in November, 1953, was double the tidal air measurement. (Fig. 8.)

CASE IX. Respiratory paralysis with quadriplegia; hirsutism and dermatitis; pyelonephritis and renal calculi; ureterolithotomy. For over two weeks M. O., a forty year old housewife, had a sore throat, pain and a tingling sensation in the legs, back pain and weakness of the left leg followed by weakness of the right leg. Nausea, emesis and a headache preceded a July 27th admission to the hospital because of respiratory distress. The fever at

that time was 102°F., the pulse rate 100 beats per minute, the respiratory rate 40 per minute and the arterial blood pressure 124 mm. Hg systolic and 90 diastolic. The alae nasae were distended, the neck stiff, the breathing shallow and irregular, and both legs were paralyzed. During the twenty-seven-hour trial of a chest cuirass respirator, preceding use of a tank respirator, both arms became paralyzed and a tracheotomy became necessary. The tracheotomy was closed again after the second week and the patient transferred back by quick steps to full time reliance on the chest cuirass respirator. From November a rocking bed was substituted for the cuirass over increasing proportions of the time. For a nine-month interval beginning in February, 1953, the time in the chest cuirass respirator was progressively reduced in favor of a small increment in rocking bed time and a large increment, up to ten hours a day, in unassisted time. Respiration became easy in the supine position but remained tiresome and difficult in the sitting position. A moderate movement of the right diaphragm and a minimal movement of the left became demonstrable by fluoroscopy. When raising the chest for inspiration she contracted the pretracheal muscles and platysma bilaterally but had no use of the sternomastoid muscles. She learned to sit up comfortably, wearing a chest cuirass respirator, and recovered enough use of the right hand to write or feed herself when supported by slings. For a year following the trauma of the initial phases of the illness this woman had a recurrent itching, peeling dermatitis of the face comparable to sunburn, and striking hirsutism of the chin, neck, arms and legs. She had no hypertension, but did develop multiple small calcifications in both renal pelves and a left renal obstruction relieved by an immediate ureterolithotomy at the end of October. She resumed use of a tank respirator continuously for the two weeks between the time of this operation and her transfer to a respirator center. A year after the onset of the illness the vital capacity measurements were of the order of 300 ml., the final reading in November being 350 for this 70 pound woman who was 5 feet tall. (Fig. 9.)

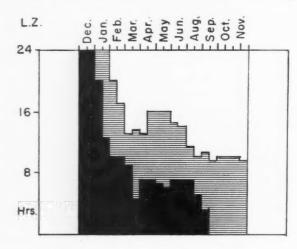
CASE X. Respiratory and skeletal muscle paralyses. For three days, W. B., a twenty-seven year old housewife, had a sore throat, headache, emesis, chills and pains in the legs and back. On the fourth day both legs became weak. On the morning of the fifth day, August 20, 1952, she

was transported 40 miles to a hospital in Lexington because of shortness of breath. She did not remember being placed in a tank respirator but became aware of surroundings about two hours later. There was no difficulty with swallowing and no tracheotomy was performed, but both arms became weak. After remaining in a tank respirator for ten weeks she transferred to a rocking bed thirty minutes a day and learned to breathe unassisted for five minutes. She then gradually shifted to the rocking bed all day and used the tank respirator at night for sleep. From the beginning of 1953 she learned to remain on the rocking bed day and night, to sleep on it and to remain unassisted for three hours. In April an upper respiratory infection made necessary a return to the tank respirator for a three-week interval followed by a return to the previous schedule. Intervals of anxiety were associated with a diminished food intake, and enemas were needed for relief of constipation. On September 23rd, when transferred to the hospital in Louisville, she appeared undernourished. There had been no acne, growth of hair, hypertension or renal calcification. She was able to breathe unassisted all day either sitting or lying supine, but a strong voluntary effort of bilaterally enlarged sternomastoid muscles was evident at each inspiration. Movement of the right diaphragm was demonstrable by fluoroscopy. The trunk and legs had remained paralyzed, but she used the fingers and could write or feed herself with the right hand. The joints were too stiff to allow a sitting position but she was able to breathe easily while strapped vertically to a standing bed half an hour a day. This 65 pound woman was 5 feet, 4½ inches tall. The vital capacity in November was 430 ml. when she was supine and 390 when she was propped up at a 50 degree angle. She had learned to breathe unassisted all day, using voluntary neck muscles synchronously with the diaphragm, but was not able to breathe subconsciously during sleep. (There is no chart of this patient's respiratory recovery.)

CASE XI. Quadriplegia with respiratory paralysis complicating previous right oleothorax for pulmonary tuberculosis. L. Z., a garment worker and mother of four children, entered the hospital on December 3, 1952, the fourth day of an illness characterized by severe headache, nausea, vomiting and pain in both legs. When examined she was dyspneic and cyanotic. The left arm and both legs were paralyzed. In a tank respirator there

was an immediate improvement in the dyspnea and cyanosis. Prior to the paralysis of the diaphragm which occurred at this time, the right side of the diaphragm had already been paralyzed temporarily, in 1949, by a crush of the right phrenic nerve and a pneumoperitoneum as treatment for active right upper lobe pulmonary tuberculosis with cavitation. After partial recovery from the phrenic operation the upper third of the right lung was permanently collapsed by means of a paraffin pack, but the patient remained in fairly good health for almost two years prior to the attack of poliomyelitis. Paralysis of the diaphragms appeared by radiography to have allowed collapse of nearly all of the remainder of the right lung, and much of the left not already encroached by a shift of the mediastinum. Although able to take only small, rapid, shallow breaths even four months after the paralysis from poliomyelitis, this patient made striking progress in use of the rocking bed and unassisted respiration over a nine-month period. She learned to sit upright in a wheelchair, supported by a corset, and to use the hands and arms for feeding and writing. The legs remained paralyzed and useless but were finally fitted with long leg braces which permitted use of a standing bed for thirty minutes daily. This patient made best progress in the final six months while on a diet which corrected her obesity. She had no dermatosis or unusual growth of hair, no renal calcification and no hypertension.

Respiratory schedule: Although admitted in respiratory failure with asphyxia, the patient was placed in a tank respirator only after a trial of a chest cuirass respirator which failed to provide adequate pulmonary ventilation. Two weeks later trials of less effective respiratory aids were resumed. From December 18th she used a chest cuirass respirator eight minutes and remained unassisted five minutes a day. By the end of the month she was using the cuirass forty-five minutes, the rocking bed eighteen, and remained unassisted ten minutes when not in the tank respirator. In February she was on a rocking bed sixteen hours, unassisted two hours, and in a tank respirator the remainder of the time. In March she used a rocking bed for two and a half to five hours a day, remained unassisted ten or twelve hours, and reduced the time in the tank respirator from eleven hours a night to seven before resuming longer use of the tank respirator at night because of fatigue. In April she alternated every two hours during the day between the rocking bed and unassisted time. In June she slept in the tank respirator from midnight to 7 A.M., spent three hours unassisted and used a tank respirator the remainder of the time. In July she slept on the rocking bed every night until 2 A.M. before being



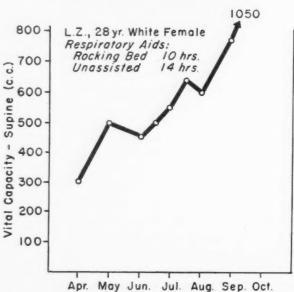


Fig. 10. Case XI. A resumption of function by the diaphragm was associated with a rapidly increasing vital capacity after four months of paralysis. The unusual progress of this overweight woman was made possible by nurses who lifted her repeatedly from the tank respirator to a rocking bed.

transferred to a tank respirator. In August, September and October she was able to sleep on the rocking bed at night and breathe unassisted during the day except for occasional rest periods of an hour in the afternoon. Although she could breathe well either sitting or lying flat, she was most at ease when propped up to an angle of 30 degrees. With each inspiration the anterior neck muscles, including the sternomastoids, were

active in raising the thorax and the abdomen moved down slightly. By fluoroscopy there was evidence of a return of function of the diaphragm which was better on the left. This young woman was 5 feet, 6 inches tall and weighed 118 pounds after reducing. The vital capacity measurements increased progressively from 300 ml. in April to 1,050 in the first week of November. (Fig. 10.)

The twelfth patient achieved part-time respiratory independence by the use of enlarging accessory respiratory muscles, and without fluoroscopic evidence of a return of diaphragmatic function. Although the anterior neck muscles so used were of the voluntary type, their use for respiration became sufficiently habitual to permit restful sleep when the action was aided by the motion of a rocking bed.

CASE XII. Respiratory paralysis with quadriplegia; anorexia and undernutrition; recovery of partial respiratory independence without diaphragm; pyelonephritis. From September 7 to 10, 1952, J. S., an eight year old girl, had malaise, anorexia and constipation. One day later, at the hospital, there was a fever of 103°F. by rectum, a respiratory rate of 45 per minute, an arterial blood pressure of 120 mm. Hg systolic and 60 diastolic. The child was confused, unresponsive and unable to sit, but vomited from time to time. The neck was stiff, the Brudzinski and Kernig signs positive; the arms and trunk were paralyzed except for a residual tremulous movement of the left hand. The loss of motor power in the legs was incomplete and for the most part transient. Following a trial of inadequate respiratory aid by a chest cuirass respirator and transfer to a tank respirator, on the first day, the arterial blood pressure reached its highest value: 150 mm. Hg systolic and 90 diastolic. There was no hypertension thereafter and the optic fundi remained normal. Although there were no catheterizations for urinary retention, there was a urinary infection by gram-negative bacilli followed, after treatment, by the presence of a few red cells and casts in the urine sediment. For the first months, as the respiratory weaning efforts were pushed, there was a continuing nervous tension with irritability, enuresis and anorexia. Voluntary feeding occurred only in the presence of a member of the family, and the nutrition remained poor for six months. From April the emotional instability and nutrition improved and she learned to walk for up to five minutes at a time while

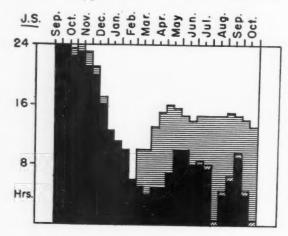
wearing a corset, although use of the hands and arms did not return. This child's skin remained unblemished and the general condition was good at the end of a year.

Respiratory schedule: After the unsuccessful trial of a chest cuirass respirator on the first day this girl remained in a tank respirator for two weeks and then began a series of trials of time on the rocking bed and time unassisted, but progress in this direction was curtailed by exhaustion, irritability and lack of respiratory muscle power. After trials of unassisted respiration, advanced from five minutes to an hour in October, she became unable to breathe unaided for two weeks but continued use of a rocking bed for two more months and was placed on a rapidly progressing schedule of unassisted time for four months. In December she had become able to remain unassisted for up to four hours a day outside the tank respirator, but had an unsuccessful three-day trial at continuous use of a chest cuirass respirator. During January and February, 1953, she remained unassisted outside the tank respirator half of the time but showed signs of fatigue. For the next eight months she progressed best when encouraged to spend approximately half the waking hours at rest on a rocking bed and a full night for sleep in a tank respirator. In March, April and May the time for sleep at night in the tank respirator was increased progressively from five to nine hours before she could be given adequate rest. In June, on a stable schedule, she alternated by day between three hours unassisted and one on a rocking bed, slept on the rocking bed in the evening and reduced time in the tank respirator proportionately. Use of a cuirass respirator was resumed for one-half hour daily in an effort to preserve or restore flexibility of the chest wall. A decision by the patient to transfer completely from the tank respirator to a rocking bed in July proved premature, as she elected frequently during the next two months to return to the tank respirator at night for better rest. In October and the first week of November, however, sleep on the rocking bed at night and in the afternoon appeared to provide adequate rest and the tank respirator was again abandoned. This girl's respiratory movements appeared to depend entirely on voluntary accessory respiratory muscles. A fluoroscopy in May had confirmed the indications from direct observation that neither the diaphragm nor the intercostal muscles were functioning. Until she reached a stable schedule permitting adequate rest throughout the day and at night, progressive fatigue of the small muscles used for respiration was reflected by a fall of the vital capacity between morning and evening. This girl learned to raise the rib cage for inspiration by means of enlarging voluntary anterior neck muscles, chiefly the sternomastoid muscles. When sitting she used muscles of the abdominal wall to aid expiration. The muscles of the posterior neck and back were adequate to balance the head and trunk. In the last half of her first year of disability the vital capacity, as measured in the morning, increased from 250 to a sustained plateau value of 300 ml. which remained consistent through the day only after the accessory respiratory muscles used had become large and less easily tired. She was 4 feet, 3 inches tall and weighed 42 pounds. (Fig. 11.)

Five patients, Cases XIII to XVII, had an extensive loss of skeletal muscle and required a long course of mechanical respiratory aid although they recovered the ability to breathe independently within a year. Because of the risk of a relapse as a result of intercurrent illness or physical exhaustion from some other cause preceding recovery of an adequate reserve of respiratory musculature, such patients need to remain within reach of mechanical respiratory aid until an ample vital capacity and absence of signs of fatigue for many months indicates a wide margin of safety. Unexpected respiratory deaths have occurred among patients of this type hastily weaned and prematurely released as independent of mechanical respiratory equipment.

CASE XIII. Respiratory paralysis with quadriplegia; hypertension; anxiety, anorexia, undernutrition, constipation, fecal impactions and diarrhea; recovery of partial respiratory independence. E. J., a twelve year old schoolboy, had fever, an occipital headache and a sense of faintness followed by generalized muscular tremors on the third day, September 23, 1952, when he was admitted to the hospital because of respiratory distress. The dyspnea and cyanosis was such that he was immediately placed in a tank respirator and had a tracheotomy. Two days later he was paralyzed from the neck down except for ability to move the toes. There was persistent cyanosis, accounted for by atelectasis of the upper lobe of the right lung and improved after a month. In the course of efforts at forced transfer from the tank

respirator to less adequate forms of respiratory aid he remained highly agitated, was considered a behavior problem and became hypertensive. From January, 1953, when the arterial tension reached 150 mm. Hg systolic and 120 diastolic, he remained hypertensive for nine months al-



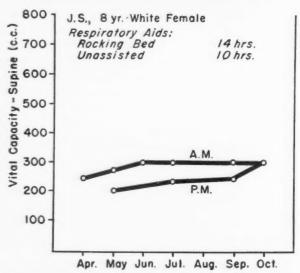


Fig. 11. Case XII. In the first six months a rapid change to unassisted time was hampered by emotional instability and fatigue. Even with more complete respiratory aid during the following year a decrease in the vital capacity between the morning and evening measurements suggested fatigue of the muscle remnants used for respiration.

though the recorded pressures gradually decreased to 120 mm. Hg systolic and 90 diastolic. However, he contracted no urinary infection and had no renal calculi. The specific gravity of the urine remained fixed below 1.013. During the first six months efforts at oral feeding produced an emotional reaction with emesis, and the degree of emaciation created the impression of a living skeleton. Constipation and fecal impactions alternated with diarrhea. There was

a convulsive seizure in February treated by diphenylhydantoinate and phenobarbital until March. After forced weaning efforts were discontinued in favor of a respiratory schedule more closely adjusted to tolerance and subjective fatigue, the appetite and bowel motility returned, the nutrition improved and the anxious, withdrawn social reaction was replaced by a warmer more confident emotional response and a novel display of initiative. The tracheotomy was closed in April following recovery of some abdominal muscle power and ability to cough. Although the hips and other joints had become stiff, he was fitted with a corset and wheelchair and learned to use a standing bed. Useful function returned in the right hand and forearm. The mental acuity was demonstrated by schoolwork and chess. There were no dermatologic complications during or after the stressful early phase of the illness.

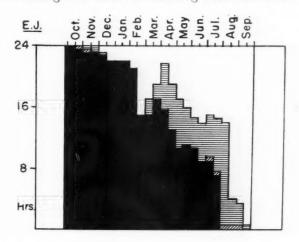
Respiratory schedule: After the initial month in a tank respirator forced trials at unassisted respiration and use of a chest cuirass respirator were undertaken. At the end of October the patient was breathing as long as fifteen minutes unassisted and was beginning trials up to onehalf hour or more with the chest cuirass and later also with the rocking bed. In February the unassisted time was increased precipitously to five and then eight hours a day, and his condition deteriorated in proportion until more adequate respiratory aid was reinstated on a schedule adjusted to tolerance and subjective fatigue. During April he slept in a tank respirator at night and alternated between unassisted respiration and use of the rocking bed every two hours during the day. In May he spent two additional hours daily unassisted. In June he rocked for an hour and remained unassisted for three hours alternately during the day, and slept on the rocking bed until midnight before transferring to the tank respirator. A chest cuirass respirator was tried one-half hour daily in an effort to limber the chest wall. At the end of July he abandoned the tank respirator in favor of the rocking bed for sleep at night. During the next two months, August and September, he became increasingly independent of the rocking bed. A year after the onset of the paralysis he had become fully independent of mechanical respiratory aid. Function of the left side of the diaphragm had been unmistakably evident for seven months by a well defined linear moving shadow, or Litten sign, over the left lower ribs.

By fluoroscopy it was confirmed that the left side of the diaphragm moved well although the right side did not. Used in the initial months continuously for unassisted respiration, the sternomastoid and other anterior neck muscles were later brought into play only as needed for an extra large forced inspiration as for a measurement of the vital capacity. This boy was 4 feet, 10 inches tall. Following a major improvement in his nutrition the weight reached 55 pounds. In the final six months of the first year of his disability the vital capacity increased from 400 to 600 ml. (Fig. 12.)

CASE XIV. Respiratory paralysis and quadriplegia followed by recovery of respiratory independence and limited use of the hands and arms. For five days R. P., a seventeen year old male student, had a low fever, pain in the neck and upper back, vomiting attacks and generalized weakness. Admitted to the hospital on September 5, 1952, because of respiratory distress, he had a fever of 103°F. by rectum, a pulse rate of 100 beats per minute, a respiratory rate of 30 per minute and an arterial blood pressure of 120 mm. Hg systolic and 70 diastolic. He was dyspneic. The alae nasae flared and the anterior neck muscles were active. The neck was stiff. With efforts at inspiration the thorax expanded only on the right side. The bladder was distended and palpable 3 cm. above the umbilicus. The patient was unable to void voluntarily. Although the cranial nerves had been spared, there was a marked weakness of all four extremities. He was placed in a chest cuirass respirator and had to be catheterized regularly for the first ten days. No tracheotomy was performed. Although afebrile after four days, he became completely quadriplegic for three weeks prior to partial recovery of the hands, forearms and right foot. The joints were kept fairly mobile but there was a striking atrophy of the forearms and legs. This patient spent much of his convalescence working with a ham radio transmitter. Following a tutoring course he was awarded a high school diploma while wearing a chest cuirass respirator at the June, 1953, commencement exercises of his class. A year after the onset of the paralysis he had been fitted with a wheelchair, had learned to feed himself when propped up and equipped with a sling for the right arm, and had learned to breathe without mechanical aid.

Respiratory schedule: After six weeks of continuous reliance on a chest cuirass respirator there was a progressive shift over nine months to

full independence from the cuirass respirator and the rocking bed. A week after entering the hospital he had become able to breathe for five minutes without aid. In May he was breathing unassisted except for two to four hours a night on the rocking bed and was making brief use of a



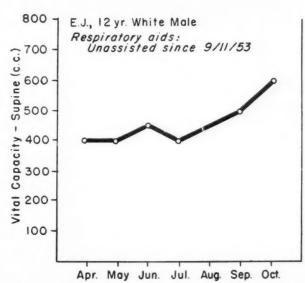
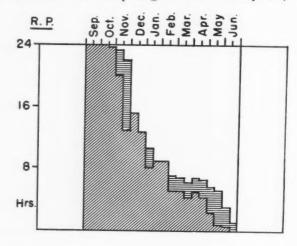


Fig. 12. Case XIII. The attempted shift to unassisted time during the first six months of the paralysis was hampered by emotional instability and fatigue until the change was undertaken more gradually by way of the rocking bed. The rising vital capacity at the end of a year led to full independence from mechanical respiratory aid.

chest cuirass respirator when he sat up for meals. All use of either the rocking bed or the cuirass was discontinued after June 23rd. Both of the sternomastoid muscles had become markedly enlarged and acted to raise the thorax when they were balanced by the weight of the head and the patient was in a supine position. When the patient was propped to a sitting position, the relatively unused and atrophic posterior neck

and back muscles failed to compensate. With each effort at inspiration the head was therefore pulled forward instead of remaining in a stable position. It was evident by fluoroscopy that this patient recovered good use of the right but not of the left half of the diaphragm. The vital capacity



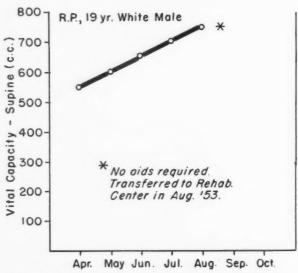


Fig. 13. Case xiv. Enough respiratory muscle was spared to permit use of a chest cuirass respirator from the beginning. Respiratory muscle exercises included daily use of the rocking bed. The vital capacity steadily increased.

as measured between April and August increased with mathematical precision from 550 to 725 ml. in the final five months preceding the independence of respiratory equipment which made him eligible for admission to a rehabilitation center. (Fig. 13.)

CASE XV. Respiratory and skeletal muscle paralysis; convulsions; recovery of respiratory independence. A. L., a twenty-two year old Negress employed as a beautician, entered the hospital on August 28, 1952, with a history of constipation, fever,

emesis and weakness of the arms for three days. The temperature was 105°F, by rectum, the pulse rate 90 beats per minute, the respiratory rate 30 per minute and the arterial blood pressure 120 mm. Hg systolic and 80 diastolic. The neck was stiff. Thoracic expansion was equal bilaterally, the respiratory rhythm was regular and there was no dyspnea. The arms were weak and the tendon reflexes of the arms and legs were absent. The Brudzinski and Kernig signs were positive. Because of respiratory distress on the third day after entry to the hospital she was placed in a chest cuirass respirator. After six days on this aid there was a convulsion classed as general although obvious only in both legs. She was afebrile after nine days but had another convulsion on the tenth before being transferred from the chest cuirass to a tank respirator. Concomitantly with the respiratory weaning schedule the patient was thereafter given diphenylhydantoinate and phenobarbital as anticonvulsant medication until March, 1953. The continuing paralysis included the arms and shoulders with the exception of an extremely weak and scarcely functional remnant including the brachioradialis, the extensor radialis, the long flexors of the thumb and long flexors of the fingers of the left hand. The muscles of the upper portion of the trunk were lost. With the exception of the right anterior and posterior tibial, function of the leg muscles was preserved or recovered at the end of a year. A fair degree of function remained in the muscles of the abdominal wall. From April onward walking trips about the ward were undertaken with the support of a corset and a long leg brace. This patient had no hypertension, renal calcification or dermatologic sequelae. Following transfer to a center for needed training she learned to dress and take meals with the aid of adaptive equipment.

Respiratory schedule: At the onset of convulsions the chest cuirass respirator initially tried was deemed inadequate and was replaced on the tenth day by a tank respirator. Within the following month, however, she returned to full time use of the chest cuirass respirator and a two-week trial of an hour a day on a rocking bed. The portion of time spent in a chest cuirass respirator was then decreased rapidly in favor of unassisted time until February, 1953, when the cuirass was replaced by the rocking bed at night, and no mechanical aid was used during the day time hours. This patient became independent of the rocking bed at the beginning of June and was

placed in a rehabilitation center at the end of that month. The respiratory musculature included the sternomastoid and other anterior neck muscles and the right but not the left half of the diaphragm. The abdominal muscles contracted to aid with expiration. The vital capacity increased from 550 ml. in May to 610 ml. in June, when she became independent of mechanical respiratory aid, and to 700 ml. when measured three months later at a rehabilitation center. The chart of the gain in vital capacity is superimposed on that of the respiratory aids used. (Fig. 14.)

CASE XVI. Respiratory and other skeletal muscle paralysis; atelectasis and pneumonia; recovery of respiratory independence. J. B., a five year old girl, had a headache, pain in the back and neck, fever and weakness. Admission to the hospital became necessary because of respiratory difficulty. The respiration had become rapid and shallow, and the thorax did not move. The neck was stiff, both arms and legs were weak, and the tendon reflexes of the extremities were not demonstrable. After three days of observation, during which the respiratory embarrassment progressed, she was placed in a tank respirator and a tracheotomy was performed. During the next four febrile months there was a succession of atelectases and pulmonary infections treated by frequent bronchoscopy through the tracheotomy for removal of purulent or mucous plugs. The flexion and extension movements of both wrists and ankles were spared, but otherwise there was no effective movement of the extremities. However, she learned to roll over in bed and to balance the head when propped in a sitting position and supported by a corset. Following transfer to an orthopedic hospital after seven months she was braced, fitted with a wheelchair and taught to walk a few steps.

Respiratory schedule: After the initial two weeks in a tank respirator this child made a rapid transfer to a rocking bed and to unassisted respiration. From the fourth month onward she used the rocking bed little, if at all, and appeared to have become independent of it. Little use was made of the sternomastoid muscles. Respiratory movements were carried out by means of the lower intercostal muscles, the left half of the diaphragm and the abdominal muscles. The vital capacity in May, 1953, when she was transferred from the respiratory ward, had reached 300 ml. At a follow-up examination in November, a month after an attack of

bronchopneumonia, it had increased to 480 ml. when measured with the patient supine or sitting in a wheelchair.

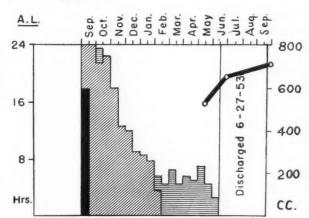


Fig. 14. Case xv. Enlarging accessory respiratory muscles and partial regeneration of the diaphragm led to independence from mechanical respiratory aid after ten months. The vital capacity increased for a longer interval.

CASE XVII. Respiratory paralysis and quadriplegia; recovery of respiratory independence and partial use of the extremities; pyelonephritis with renal calculus, ureterolithotomy. D. H., a thirty year old housewife who entered the hospital on July 28, 1952, because of dyspnea, had been prostrated by the death from poliomyelitis of a three year old son six days earlier. For four days she had a headache, backache, fever and vomiting attacks, and for one day numbness with a tingling sensation of the hands and feet and progressive shortness of breath. Although told she had a rheumatic heart, she remembered no rheumatic fever. The rectal temperature was 102°F., the pulse rate 96 beats per minute, the respiratory rate 32 per minute and the arterial tension 120 mm. Hg systolic and 80 diastolic. She became unresponsive and was believed to be moribund. The major skeletal muscle groups were weak and the tendon reflexes weak or absent. At the cardiac apex an easily audible systolic murmur was transmitted to the axilla and back. The spinal fluid contained 40 lymphocytes per cu. mm. and 72 mg. of protein per 100 ml. After a twelve-hour trial in a chest cuirass respirator which proved inadequate she was transferred to a tank respirator and a tracheotomy was performed. The fever continued for two weeks, after which the arms were partially and the legs completely paralyzed. The tracheotomy was closed for four days but reinstated. In the following months there was a refractory mixed urinary infection and a series

of bouts of bronchopneumonia. There was no hypertension but in March, 1953, following gross hematuria, a calculus was removed surgically from the left ureter. Over another two months of waiting for admission to a rehabilitation center she undertook to feed herself with the left hand, to walk with a body brace and long leg braces, and to go home for short visits. This woman developed the usual stiffness of the extremities, particularly of the shoulders. The entire right arm and the upper portion of the left arm remained of little value but there was a fair recovery of strength in the left hand and forearm. There were joint fixations and contractures of the fingers of both hands. The entire left leg and the lower portion of the right leg remained paralyzed.

Respiratory schedule: Over a six-month interval there was a rapid two-month shift from use of a tank respirator to use of a chest cuirass respirator, and a somewhat less swift transfer, most of it in four months, to unassisted respiration. Little use was made of the rocking bed. After seven months the ability to cough had returned and the tracheotomy was closed. Respiratory movements were aided by hypertrophic sternomastoid muscles and other anterior neck muscles, but not by intercostal muscles. Atrophy of the intercostal muscles left the ribs unusually prominent. The recovery of function of the diaphragm, as noted by fluoroscopy, was good on the left and partial on the right. In April and May, after freedom from dependency on mechanical respiratory aid for five months, the vital capacity measurements reached 700 and 750 ml.

CASE XVIII. Respiratory paralysis with quadriplegia; hypertension; gastric dilatation; rapid recovery of partial respiratory independence. R. M., a sixteen year old schoolgirl, had a headache, fever and sore throat for two days. Unable to walk unsupported, she was admitted to a local Kentucky hospital. One day later the hands and arms were tingling, both arms were weak and the voice was nasal. From the fourth day inability to void was relieved by an indwelling catheter. Dyspneic on the fifth day, September 17, 1953, she was moved 240 miles by ambulance to the hospital in Louisville, where she arrived in obvious respiratory difficulty. The rectal temperature was 102°F., the pulse rate 120 beats per minute, the respiratory rate 32 per minute and the arterial pressure 120 mm. Hg systolic and 80

diastolic. The respiration was rapid and shallow but regular, the speech jerky and reluctant. Swallowing was a slow process. The neck was stiff. Paralysis of the arms and legs appeared complete except for the fingers and toes. The blood count was within normal limits but there was pyuria. The cerebrospinal fluid collected on the fourth day of illness contained 56 lymphocytes and 4 polymorphonuclear leukocytes per cu. mm. and 65 mg. of protein per 100 ml. There was a possible glove-stocking hypesthesia of short duration. There was a transient arterial hypertension which reached 140 mm. Hg systolic and 100 diastolic, and subsided again in the first week concomitantly with generalized intractable muscular pains. Nourishment was well taken after two days. The urinary infection was controlled after the first week. After a month a five-day interval of gastric distention made gastric aspirations and parenteral fluid therapy necessary. After two months the respiratory recovery was progressing uneventfully when arrangements were completed for transfer to an established center for respiratory care and rehabilitation.

Respiratory schedule: Immediately after she reached the hospital the patient was placed in a tank respirator, although she had not yet reached the stage of complete respiratory paralysis and could breathe for five minutes at a time without assistance. After six days on the ward and four without fever she was encouraged to transfer at will, over increasing intervals, from the tank respirator to a rocking bed. After a week of such trials the rocking bed was preferred for continuous use although the chest cuirass respirator was donned for one-half hour a day as an exercise. In October the respiration was unassisted for an hour and then for two hours a day. In the first week of November the unassisted time had lengthened to two and a half hours three times a day, the time in the cuirass to two hours a day, and the remainder of the day was passed on the rocking bed. Respiratory movements were carried out by the right half of the diaphragm and by voluntary anterior neck muscles, particularly the sternomastoid on each side. The vital capacity measurement for this 5 feet, 71/2 inches tall girl climbed from 400 ml. on September 17th, the date of admission, to 480 on October 9th and 580 ml. on November 9th.

CASE XIX. Partial respiratory and other skeletal muscle paralysis; early recovery of respiratory inde-

pendence. B. C., a four year old girl, had fever, headache, anorexia and constipation for five days, and entered the hospital on September 2, 1953, when the left leg buckled and she became unable to stand. The rectal temperature was 101°F., the pulse rate 140 beats per minute, the respiratory rate 50 per minute and the arterial tension 90 mm. Hg systolic and 70 diastolic. The child was alert but irritable, had a weak cry and was unable to sit up. The respiration was rapid, regular and shallow, and the patient appeared exhausted. She had a stiff neck. Deep tendon reflexes were demonstrable only in the left biceps and triceps muscles, and the extremities were weak although the soles of the feet could be flexed and the toes moved. Mechanical respiratory aid became necessary. The fever reached 103°F. but subsided after three days. The left arm became weaker than the right although movement of the forearm and hand was not entirely lost. There was transient unexplained hematuria. Following the acute stage stretching exercises, particularly for the hamstring muscles, bracing and muscle re-education were initiated, to be continued at a local orthopedic hospital to which she was transferred after fifty days of emergency care.

Respiratory schedule: In view of the obvious signs of diminishing respiratory muscle power this child was placed in a tank respirator on the day of admission. She had no swallowing difficulty and needed no tracheotomy. Intervals of up to fifteen minutes of unassisted respiration were allowed from the first day and up to six hours after the third day. After the first week she began a transfer to the rocking bed but spent eight hours a night in a tank respirator before completing the shift. At the same time the schedule of unassisted time was advanced at a rate such that no mechanical aid at all was used after the first month. At the time that she became independent of such aid it could be seen by fluoroscopy that she had recovered good use of the left but not of the right leaf of the diaphragm. Use of accessory respiratory muscles was not evident. A satisfactory measurement of the vital capacity was not obtained.

CASE XX. Partial and asymptomatic decrease in respiratory capacity followed by rapid recovery; partial paralysis of the extremities. E. L., a twenty-two year old housewife, had increasing pain in the back and legs for five days until admitted to a hospital on March 29, 1953. She had a left occipital headache, weakness of both legs and

was unable to walk. The rectal temperature was 101°F., the pulse rate 90 beats per minute, the respiratory rate 24 per minute and the arterial blood pressure 110 mm. Hg systolic and 90 diastolic. The neck was stiff. The right leg was partially and the left leg extensively paralyzed. The abdominal reflexes and the knee and ankle tendon reflexes were absent. The spinal fluid contained 180 lymphocytes per cu. mm. This woman became afebrile after a day and regained partial strength of both legs in ten days, sufficient to permit a test of ability to stand and take a few steps. At the same time she had pain and lost strength in the arms and shoulders. There was no demonstrable impairment of respiratory function except that the vital capacity increased progressively in ten days from 1,550 to 1,650 ml. After two weeks of care and observation of the acute phase of the illness there appeared to be no further threat of respiratory paralysis and she was therefore transferred to a local hospital for orthopedic management of residual paralyses of the trunk and extremities.

COMMENTS

Examples of arrested, slow and rapid respiratory recoveries have been presented. When either a retarded or rapid recovery occurred, it appeared to come about independently of hasty effort to break presumed psychologic or biochemical addiction from chronic overventilation or presumed emotional dependency on some particular mechanical respiratory aid. Even the four most physically limited respiratory cripples of this series did not hesitate, when helped by trusted attendants, to change to other mechanical respiratory aids or to try unassisted respiration. Unfamiliar types of mechanical respiratory air were regularly accepted as soon as the patient, secure in a tank respirator, discovered by trial that such other aids as tank respirator positive pressure dome attachments, cuirass respirators or rocking beds could be adjusted to provide pulmonary ventilation adequate for comfort. Failures did occur, with clock-like regularity, when the ventilation provided was either insufficient or dependent on sustained effort leading to exhaustion. Although the presence or absence of subjective dyspnea was the most immediately useful bedside guide, tidal air measurements also served as a convenient objective basis for estimating the adequacy of mechanical aids. For evidence of fatigue the subjective estimate by the patient

was most helpful and well correlated with the corroborative objective signs of emotional lability and rapidly decreasing vital capacity measurements. Early efforts at precipitous muscle re-education, based perhaps on supposition that exercise must be carried to exhaustion if it is to lead to muscular hypertrophy or retraining, did not appear justifiable. When a regular schedule of well tolerated daily exercise was allowed alternately with ample rest periods well within the limits of fatigue, there was uneventful recovery of respiratory muscle function and other muscular functions which progressed uneventfully to the extent that re-innervation or gradual enlargement with use permitted.

The most adequate as well as the less adequate mechanical respiratory aids, when used by the patient as a supplement to periodic voluntary respiratory effort alternating with rest, allowed gradual development of secondary hypertrophy of needed respiratory muscle where potentially useful muscle remnants existed. Short but gradually increased transfers from the tank respirator, up to several times a day, both to the rocking bed and to unassisted time, under close supervision, appeared to expedite best the rate of real lasting recovery based on a return of muscle power rather than transient psychologic or biochemical overventilation influences.

Premature withdrawals of adequate respiratory aid at an early stage were followed by exhaustion, collapse and a delay in recovery reflecting wishful, compulsive behavior in the effort to "wean" a patient from psychologic or biochemical dependency on his aid. It became apparent that efforts at forced weaning or endurance tests lead to exhaustion, asphyxia and panic, just as sneak withdrawals of full aid by surreptitious reduction of tank pressures or rates lead to a loss of confidence when discovered by the patient. No useful purpose can be offered for forcing or misleading the respiratory cripple. Graded respiratory activity schedules worked best by far when regularly reviewed by the doctor in direct consultation with the patient and drawn up specifically within the limits of the patient's own estimate of his ability. It thus became possible for the patient to assume the initiative in his own interest, leaving the physician the role of balancing or restraining rather than pushing.

SUMMARY

Over 1,000 young adults and children have recently survived the acute stage of poliomyelitis in the United States only to be left with permanent or protracted respiratory muscle paralysis with more or less complete quadriplegia. Through realistic and timely planning much can actually be offered these severely disabled patients. Mental function, emotional stability and a useful place in the world are practical goals for specialized total care providing help with elementary medical and social complications, mechanical respiratory aids and graded respiratory muscle reeducation coordinated with training to other adaptive equipment compensatory for lost muscle functions. Twenty illustrative cases exemplify management problems and respiratory recovery rates with degrees of paralytic respiratory disability ranging from extreme to minimal.

Seminars on Antihypertensive Drugs

Rauwolfia in the Treatment of Essential Hypertension*

ROBERT W. WILKINS, M.D.

Boston, Massachusetts

THE introduction of Rauwolfia into the medicinal armamentarium against essential hypertension signalled a new approach to therapy of the pathologic physiology of this disease. Previously those who had been interested in the drug treatment of hypertension had been absorbed in a trial of agents designed to alter markedly, not to say drastically, the vasomotor control of blood pressure. A number of drugs were available which were capable of blocking the whole autonomic nervous system, or at least the adrenergic responses, either in the periphery or in some more central location. Other agents were evolved which produced active vasodilatation either neurogenically or by direct action upon the smooth musculature of the vessel walls. All these agents, regardless of the site of their action, had in common an ability to lower blood pressure markedly, even to collapse levels, and usually did so immediately or at least shortly after their administration. While many of them had side reactions which were undesirable, it was generally agreed that these would have to be accepted if necessary to obtain the blood pressure-lowering action. Occasionally the thought was expressed that perhaps too great a hypotension particularly in the upright posture was not a desirable effect but it was rarely doubted that profound vasodilatation occurring within minutes would be a prime characteristic of any drug useful for the treatment of hypertension.

Rauwolfia was introduced into the field of hypertension from psychiatry in which it had been long used in the treatment of disturbed mental patients. In such cases it was noticed that a fall in blood pressure and pulse rate were common side effects of the "tranquilizing action" of Rauwolfia and indeed the drug was stopped in many such patients because of these "undesirable side effects." However, Indian internists working on hypertension seized upon these side actions as possibly useful for the treatment of high blood pressure They observed, and all subsequent workers have confirmed, that Rauwolfia is not a sudden or powerful hypotensive agent but rather a very gradual, mild hypotensive drug which seems to alter the fundamental physiology of the body only very slowly, and certainly does not produce profound vasodilatation or serious interference with vasomotor reflexes such as the normal responses to the upright position. Because its action is so slow to appear (requiring three to six days) and to disappear (requiring three to six weeks), it was readily conceded that the drug might act through some intermediary mechanism. Indeed, because it has a definite sedative-like or tranquilizing effect on the emotions, many workers believed that it acted upon the blood pressure solely through this quieting effect. Several other actions, however, particularly bradycardia and its additive, if not synergistic, blood pressurelowering effect when given in conjunction with the usual more powerful hypotensive agents convinced those using Rauwolfia that it had peculiar merits of its own as a therapeutic agent for essential hypertension.

COMMENTS ON RAUWOLFIA

Forms. Rauwolfia serpentina or Ophioxylon serpentinum is an erect, attractive bush with shiny green leaves and pinkish flowers that grows to about 3 feet in height in the foothills of certain portions of India. It has a long, tapering root resembling a snake, popularly called "snake root," which contains most of the medicinal properties of the plant. The root is

* From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

pounded into a yellow powder by the natives who use it to treat a great number of illnesses. However, as already mentioned, its principal use in India is for the treatment of insane, par-

ticularly manic, patients.

Numerous efforts to extract and purify the active principles of the drug have culminated successfully in the preparation of the alseroxylon fraction containing the active alkaloids, and in the separation of the pure alkaloids, reserpine and rescinnamine. The action of these several preparations is clinically very similar provided equivalent dosages are used (i.e., 100 mg. of the crude root,* 2 mg. of the alseroxylon fraction† and 0.1 mg. of reserpine 1). While various claims have been made for the greater efficacy of one of these preparations over the others in the treatment of hypertension, there is no convincing clinical evidence in support of these claims. It is interesting to note here that whereas in India the drug came into the cardiovascular field from the psychiatric, it is now reversing that path in the United States where it was introduced as a treatment for hypertension.

Action. While it has a peculiar "tranquilizing" or sedative-like effect, Rauwolfia is not a narcotic. It will not put patients to sleep but rather will allow them to go to sleep if the occasion is propitious. It calms or decreases the reactivity of both man and animals, lessening their irritability, anxiety and aggressiveness when disturbed. These effects denote that it has an action upon the brain but in therapeutic doses this does not appear to be upon the cortex of the brain, at least as indicated by electroencephalograms, or the ability to think clearly and exercise good judgment. Its central nervous action rather is supposed to be in the mid-brain where it has certain "adrenergic blocking" effects. These include production of nasal congestion, presumably from turbinate vasodilatation, a tendency to miosis and ptosis of the eyelids particularly in animals, and may be responsible, in part at least, for the bradycardia which is a prominent action of the drug in both man and animals.

* Raudixin® manufactured by E. R. Squibb and Sons, New York City.
† Rauwiloid® manufactured by Riker Laboratories,

Inc., Los Angeles, Calif.

An additional side effect of Rauwolfia is to increase the motility of the bowel, causing a certain urgency, if not frequency, of fairly normal stools. It also causes or promotes a gain in weight, which has been variously attributed to increased appetite and to decreased expenditure of energy in "nervous" hyperactivity. In excessive dosage the drug can cause disturbed sleep with nightmares or vivid dreams, and it can also produce a state of depressed, trembly or "jittery" anxiety. Decreasing or stopping the dosage quickly relieves these side effects. In men Rauwolfia causes a decrease in libido or sex drive but this effect is not seen in women. This is definitely a lack of interest or desire and not impotence since young men may father children on this drug and animals show no decrease in fertility when taking it. Women have no change in menses or other sexual characteristics while taking the drug.

In hypertensive patients the most marked clinical effect of Rauwolfia is to improve the symptoms of which these patients frequently complain. Thus the typical hypertensive patient will lose much or all of his irritability, compulsiveness and anxiety, along with other neurotic symptoms such as nervousness, "wooziness," dizziness, palpitation, insomnia and headache. If Rauwolfia had no other effects on hypertensive patients than to relieve such complaints it would probably remain in the medicinal armamentarium against this disease. As already mentioned, however, Rauwolfia has a definite though gentle, slow hypotensive action which requires three to six days to appear and three to six weeks to reach its maximum effect. Similarly, on stopping the administration of the drug one to six weeks may pass before its hypotensive action disappears. Because of this slow action the effectiveness of the drug should not be judged in less than three and preferably six weeks of continuous administration.

Dosage. Rauwolfia may be given orally one to four times a day. The usual single starting doses are: of the crude root, 100 mg.; of the alseroxylon fraction, 2 mg.; and of reserpine, 0.1 mg. given one to four times a day. The time of doses may be suited to the patient's preference or may be arranged so as to coincide with other medications to be given. By varying slightly the time of a dose some of its relatively minor side effects can be obviated. For example, if the patient wishes to have a lesser daytime sedative effect, the whole dose of Rauwolfia may be taken at bedtime. If, on the other hand, he complains

[‡] Serpasil® manufactured by Ciba Pharmaceutical Products, Summit, N. J.; serpiloid®, Riker Laboratories, Inc., Los Angeles, Calif.; reserpoid®, The Upjohn Company, Kalamazoo, Mich.; rau-sed®, E. R. Squibb and Sons, New York City; crystoserpine®, Smith-Dorsey, Lincoln, Neb.

of vivid dreams or nightmares these may be relieved by giving the doses earlier in the day, oftentimes without reducing the total daily amount. If a patient has a particularly irritating or annoying job and wishes to have his reactivity to this lessened during the daytime, the total dose may be taken at breakfast.

Many workers advocate starting the patient on a large initial dose of Rauwolfia, e.g., 200 mg. of crude root, 4 mg. of alseroxylon or 0.25 mg. of reserpine up to four times daily, and then reducing this dosage one to four weeks later when the latent action of the drug has appeared. Certainly if such high dosages are continued over many weeks they will cause a number of patients to have over-dosage effects, the most distressing of which is depression. Therefore we have usually recommended the smaller starting dosage and even then have cautioned patients against the slow appearance of "cumulative" effects, for which one interrupts or reduces the total daily dosage.

Indications. Rauwolfia alone is most useful as a hypotensive agent in mild, labile, psychoneurotic hypertensive patients with tachycardia and symptoms of headache, palpitation, nervousness, irritability or anxiety. At the minimum it should relieve the latter symptoms and in onehalf of such patients it will restore the blood pressure and pulse rate to normal. Some adjustment of dosage may be necessary to obtain the maximum of hypotensive effects with a minimum of side reactions but at a range of 100 mg. to 400 mg. of crude root, or its equivalent, a day the ordinary patient has no serious difficulties with the drug. On the contrary, he usually is very enthusiastic about his subjective improvement. This consists not only of relief of headache, palpitation, "butterflies in the tummy," irritability and anxiety but also includes the peculiar "tranquilizing" action of Rauwolfia and its release from a sense of compulsiveness. Thus patients will state, "I no longer have to clean up the house before I go to work," or "I can let dust sit on the furniture without its bothering me." Frequently they will state, "I feel so relaxed," or "This is the way I wanted to feel." A common remark is, "I can't remember when I had a headache." Not only is there subjective improvement on Rauwolfia but often there is also objective evidence in the blood pressure and pulse rate readings of a steadying of the vasomotor reactions to the stresses and strains of life. In such labile patients one often gets the impression that the drug merely decreases the

lability of the blood pressure and "allows the patient to walk into the office with the pressure and pulse that he used to walk out with after an hour of reassurance and psychotherapy." Depending upon one's view of the natural course of hypertensive cardiovascular disease this is a more or less important achievement.

The best use of Rauwolfia is as an adjunct or background agent given in combination with the stronger drugs particularly veratrum, hydralazine and hexamethonium. After it has been given for some weeks in the same dosage as in milder cases but without satisfactory results, the other drugs are added to it, but only if and when this is proven necessary. Thus the routine plan of treatment in any hypertensive patient is to start him on Rauwolfia and, depending upon his response within three to six weeks, to continue, or to add another more powerful agent to the regimen.

In this role as a background or adjunct agent Rauwolfia not only acts additively but may also act synergistically with the stronger drugs to lower blood pressure. Certainly it can be shown that the changes in blood pressure on the same dose of a more powerful drug are greater when Rauwolfia is used in combination with it. However, the benefits of such combination drug therapy include not only a potentiation of the hypotensive action and a moderation of the general effects of the other drugs but also a counteraction against some of the unfortunate side effects of the other drugs. Thus, for example, it will considerably lessen the nausea and vomiting of veratrum and at the same time allow this drug to be used in larger doses than is possible alone without producing these symptoms. Furthermore, Rauwolfia in combination will cause a greater lowering of blood pressure without nausea or vomiting than when veratrum is used alone. Similarly, the constipating or even obstipating effect of hexamethonium is considerably moderated by the stimulating action of Rauwolfia upon the motility of the bowel. Through its bradycardic effect it also offsets the tachycardia and palpitation of hydralazine. Finally, by lessening the reactivity of the patient to all types of irritation, Rauwolfia smooths the course of drug treatment so that it seems considerably less troublesome than when Rauwolfia is not used.

Rauwolfia has a third important use. This is as a continuing agent when, as the result of a combination with stronger hypotensive drugs, the blood pressure has come to or toward normal

and the physician wishes to discontinue the stronger agents. Thus after a period of normotension it is almost always possible to eliminate veratrum, and often possible to eliminate hydralazine, from a hypotensive drug schedule. It is always considered wise to reduce or omit hydralazine and hexamethonium from a hypotensive regimen whenever possible. Therefore, after some weeks or months of a considerably lower and stable blood pressure in a hypertensive patient each of the stronger drugs is reduced in turn and eventually is omitted if this can be done without a rise in pressure. In such a situation Rauwolfia frequently will hold the blood pressure at a lower level when it was not capable initially of lowering the pressure to that level without the addition of the stronger agents. It is interesting, however, that in no patient has it been possible to eliminate a Rauwolfia preparation altogether from a medicinal regimen for essential hypertension. Continued but often very small doses (e.g., as little as 0.05 mg. of reserpine a day) appear to be necessary to keep the blood pressure at its new lower level.

There is a final important indication for the use of Rauwolfia, or at least for consideration of its use. This is in cases of very mild labile blood pressure which could not as yet be considered really hypertensive. If such "prehypertension" occurs in the offspring of hypertensive parents who have done poorly, one might consider the use of Rauwolfia as a "preventive" measure. While the wisdom of such use could not be supported by statistical evidence at the present time, Rauwolfia appears to be the ideal agent to try if the physician wishes to undertake such an experiment. The drug can be used in small doses in such situations and can be continued apparently indefinitely without harmful effects. There is no evidence that addiction, tolerance or any other deleterious effect occurs with such chronic usage of this drug. A number of young prehypertensive patients have taken Rauwolfia upwards of four years with continuous control of the blood pressure at normal levels without any apparent harmful effects.

MANAGEMENT OF CASES AND RESULTS

New and unselected office or clinic patients with essential hypertension routinely have received the following studies for grading their hypertensive disease: complete history, physical examination, urine analysis, serum NPN and PSP tests, electrocardiogram, chest and kidney

roentgenogram, cold, posture and sedation tests. These studies were made not only to assess the current condition of the patients but also to serve as a basis for comparison of the status after no treatment or drug therapy. After a period of observation of several weeks with no medication they were given either a placebo, a tablet of phenobarbital or the active drug in identically appearing pills for several weeks. The procedure was then reversed or alternated, and observations were made of the effects of these several agents, including the crude root, the alseroxylon fraction and the pure alkaloid reserpine.

In thirty-nine such patients the average of all their control blood pressures during the pretreatment period was 192/112 with the average pulse rate 82. On treatment with crude Rauwolfia the averages were 165/95 and 70. In twentyseven patients who were treated with placebos the control averages were 196/115 and 84, while the treatment averages were 186/111 and 84, respectively. In fifty-eight patients given the pure crystalline alkaloid, reserpine, control averages were 191/109 and 85 and the treatment averages 167/94 and 75. Thus it can be seen that the crude root and the pure alkaloid reserpine produce almost identical effects. The total alseroxylon fraction also gave very similar results.

In hypertensive patients in whom such a trial of a Rauwolfia preparation alone had no, or an insufficient, hypotensive effect after six weeks, a more potent hypotensive drug was then usually combined with the Rauwolfia. These more powerful drugs included veratrum, hydralazine and hexamethonium. Recently pentapyrrolidinium* has also been tried. It should be emphasized that the Rauwolfia preparation was continued. Thus the usual plan after trying Rauwolfia alone unsuccessfully for six weeks was to add either hydralazine if the pulse rate was slow (below 80) or veratrum if the pulse rate was still rapid, in gradually increasing doses if necessary, and as tolerated by the patient. Still later, in some cases, all three drugs, namely, Rauwolfia, veratrum and hydralazine, were given together in increasing ("titrated") doses as necessary and as tolerated by the patient. If after several weeks of all three drugs together in maximum tolerable dosage there was insufficient improvement, hexamethonium was added, if it

 $^{{}^*}$ Ansolysen ${}^{\tiny{\textcircled{\tiny 0}}}$ manufactured by Wyeth Laboratories, Philadelphia, Pa.

was still deemed necessary to get a hypotensive result at any cost.

The decision whether to use hexamethonium was not based solely on the blood pressure level but also upon the severity of the associated cardiovascular renal disease and especially upon the evidence of its rate of progression. When the course was judged to be malignant, namely, associated with papilledema and hemorrhages in the retinas, and to be rapidly progressive, hexamethonium was usually used. If, on the other hand, severe uremia was present, the administration of hexamethonium was undertaken cautiously if at all because the drug is eliminated by the kidneys and might accumulate in dangerous amounts when renal function is markedly impaired.

Hexamethonium therapy was usually instituted in the hospital although in occasional patients who were well indoctrinated in the oral use of drugs it could be given on an ambulatory basis. Patients were warned of its side effects particularly concerning the postural hypotension and danger of fainting. They were also instructed as to how to avoid constipation. Usually this could be taken care of by a mixture of one-half mineral oil and one-half milk of magnesia taken at bedtime in amounts sufficient to produce a morning bowel movement. Unless the patient were a doctor or a nurse, or the relative of such a professional person, he was not asked to record home blood pressures or to manage his dosage accordingly. This avoided the anxiety that such attention to the blood pressure readings per se usually produces, and also lessened the patient's tendency to change the medication because of any slight deviation in his pressures.

In 137 patients in whom Rauwolfia alone had not been satisfactory initially in controlling the blood pressure, and in whom additional hypotensive agents were then added to the regimen, the control blood pressures before any treatment averaged 204/119 and the pulse rates 86. After combination treatment of some kind the averages were 163/94 and 73, respectively. It is interesting that forty-five of these patients (about one-third) were finally maintained satisfactorily on Rauwolfia alone. That is to say, the other drugs, though initially required, were omitted from the maintenance schedule. In this group of forty-five patients the average blood pressures and pulse rates before any treatment were 192/109 and 85, whereas eventually on Rauwolfia alone they were 158/89 and 70, respectively. Forty-two of the patients had to be maintained on hydralazine as well as Rauwolfia; their control blood pressures and pulse rates before treatment averaged 204/119 and 85, whereas on treatment they averaged 157/91 and 74, respectively. Sixteen patients required treatment with three drugs, Rauwolfia, veratrum and hydralazine. Their control averages were 206/122 and 83 and their treatment averages 173/96 and 75, respectively.

Twenty-eight of the 137 patients had to be maintained on hexamethonium therapy which was added to one of the other regimens. That these were more severe cases is shown by their control average blood pressures of 227/136 and pulse rate of 87 whereas on treatment their averages were 179/108 and 74, respectively. Only a few patients, six in number, who were not satisfactorily controlled on Rauwolfia alone were so controlled when veratrum was added. Their control average blood pressures were 179/115 and pulse rates 88 whereas on treatment their averages were 153/92 and 76, respectively.

It should be emphasized here that the blood pressure readings when so averaged constitute merely the easiest of the objective signs of improvement of hypertensive disease to record. They are neither the most important nor necessarily the most satisfactory sign of improvement. Changes in eyegrounds with disappearance of papilledema, hemorrhages and finally of exudates were certainly some of the most striking evidences of improvement when they occurred. Changes in strain patterns in the electrocardiogram and lessening of the evidences of congestive failure were more frequent and often very striking. It should be emphasized also that many patients felt much better, even when previously they might have had few well defined complaints. This improvement was all the more striking when one realizes that hypertension is supposedly an asymptomatic disease. Thus patients who had complained very little would say, "I didn't realize how badly I was feeling until I began to feel better." When, on the contrary, definite symptoms such as headache, palpitation, fatigue, anxiety and the like were relieved, it was even more satisfying. To delineate or record in detail the varied improvements that took place in the clinical course of such hypertensive patients on such treatment would prolong unduly this account. Suffice it to say here, the symptomatic improvement, especially on Rauwolfia, was most heartening.

It must be admitted that some of the complications of the drug therapy were serious enough to offset its good effects on blood pressure. These have been detailed elsewhere as regards the chief offenders, namely hydralazine and hexamethonium. One can say, on the other hand, that Rauwolfia produced no serious or toxic reactions of its own and very few about which the patient continued to complain. For example, even the nasal stuffiness tended to remit after some months of treatment. Also, by carefully adjusting the dosage other side effects such as diarrhea, dreams, nightmares or depression could be relieved. Furthermore, as already mentioned, Rauwolfia could be used to moderate considerably the unpleasant effects of the other hypotensive drugs. For these reasons there seem to be few if any absolute contraindications to the use of Rauwolfia in hypertension. Only rarely have patients stopped taking it altogether and this has usually been because of the symptom of dryness of the nasal and upper respiratory passages.

Three cases illustrating the use and effects of Rauwolfia in essential hypertension are presented.

CASE REPORTS

Case I. D. F., a white male business executive, was first seen at age thirty-three for routine physical and laboratory examinations arranged on a yearly basis by his company. The patient had no complaints except for intermittent headaches. The family history and past history were non-contributory. The blood pressure was 130/75 and aside from moderate obesity there were no abnormal physical or laboratory findings. It was noted at the time that the patient was nervous, had a lot of push and ambition, and was impatient to get ahead.

He was not seen again until two years later. He had been well in the interval except for a case of "nerves," and the blood pressure was again 130/85. One year later he was seen for the third time and still complained of nervousness at times. On this occasion the blood pressure was 145/100 and the heart on physical examination was questionably enlarged to the left. The fundi were normal and studies of the urine, blood, electrocardiogram and x-ray of heart and lungs were again normal.

He failed to come in for his next yearly examination and was seen after a two-year interval during which time he had been well. On this occasion the blood pressure was found to be 160/100 and the fundi revealed definitely small and tortuous arteries but no AV nicking. All laboratory studies were normal. One year later the patient reappeared for his fifth examination, six years after his initial one. He had no complaints, but his blood pressure was now 170/100 and pulse 84. The fundi again revealed tortuous, narrow arteries which showed variations in caliber suggesting spasm. However, all laboratory studies were within the normal range.

Because of the finding of a gradual but progressive rise in blood pressure over a three-year period in this thirty-nine year old man it was decided to try small amounts of Rauwolfia. Consequently he was given 2 mg. of the alseroxylon fraction morning and night. Two weeks later the blood pressure was 140/85, pulse 84. The patient stated that he felt much more relaxed. "It's wonderful, I don't feel let down; I have just a nice, smooth feeling of well-being. I drive as hard as I used to but it doesn't bother me as much for some reason. I feel more like I used to when I was younger in college and free-lancing around. I get just as much done but I take things a lot easier."

Two weeks later the blood pressure was 125/75 and the dosage of Rauwolfia was cut to 2 mg. of alseroxylon at bedtime. Two months later the blood pressure was 110/65, pulse 76. The patient stated, "I don't have any headache or eyeache at all now. I can do anything I want to do." The dose of alseroxylon was again reduced to 1 mg. at bedtime. A month later the blood pressure was 115/75, pulse 68. There was a decided change in the appearance of the arteries of the retina. They were normally tortuous, showed no localized spasms and their caliber was normal.

Six months later the patient was again seen and said that he still felt fine. He again said, "I can drive as hard as ever, but it doesn't bother me." The eyegrounds were normal. Blood pressure 115/65, pulse 80. The patient is now maintained on alseroxylon 1 mg. morning and night. This case illustrates the symptomatically beneficial and moderately hypotensive effects of Rauwolfia in early, or "pre," hypertension.

Case II. S. B. is a thirty-nine year old businessman who was referred by his local physician for high blood pressure. His family history was not contributory except that all of his family were emotional. He had just gone into a new business entirely on his own for the first time and had done a great deal of rushing and travelling.

Furthermore he had just had his fifth child and was very concerned about his wife's health since they had planned to have only three children.

One year previously the blood pressure had been "about 200" and his local doctor had started him on a strict salt-free diet. The blood pressure had moderated to about 170 but then had returned to its previous level.

He was a moderately obese but well appearing man of thirty-nine. The blood pressure was 200/ 120, pulse 85 and the fundi showed prominent veins, tortuous arteries but no AV nicking or other abnormality. He was admitted to the hospital for study. On admission the blood pressure was 210/135, pulse 95, but in the hospital the resting blood pressure moderated to as low as 170/130. During the sedation test it dropped to 140/90. Urine showed 1+ albuminuria, otherwise normal. Serum NPN 31 mg. per cent. PSP excretion test showed 36 per cent of the dye excreted in the first fifteen minutes and a total of 88 per cent in two hours. The electrocardiogram showed abnormal T waves suggesting myocardial strain. However, the heart on x-ray was normal in size and shape. The lungs were clear. The patient was discharged on Rauwolfia 100 mg. of the crude root morning and night.

He returned one week later for a checkup at which time the blood pressure was 175/95, pulse 68. One week later, or two weeks after starting the medication, he came in stating that he felt much more relaxed. He had noticed particularly that he was not as constipated. Blood pressure was 140/85, pulse 64. Two months later the patient came in "feeling fine," with a blood pressure of 160/90, pulse 64. One month after this blood pressure was 130/80, pulse 64.

Still another month later, or five months after the start of treatment, the blood pressure was 135/80 and the pulse 68. The patient had been to a convention and thought "the blood pressure should be up." However, he felt fine and he was advised that his blood pressure was now normal and that he could stop taking the drug. He returned after one week, and the blood pressure was 155/100, pulse 84. However, he felt well. In view of the moderate rise in blood pressure, Rauwolfia was reinstituted 100 mg. morning and night as before. Six weeks later the blood pressure was 125/75, pulse 64 and the patient was feeling well. He stated, "I had to keep all the kids indoors with

me yesterday on a rainy Sunday and I got along fine."

The patient was then lost sight of for eight months when he returned for a checkup. His blood pressure was 210/110, pulse 84. He had not been taking any medicine but he had felt well. The fundi showed minimal AV nicking and slightly increased light reflex from the arteries. A placebo of Rauwolfia containing phenobarbital was started morning and night. Unfortunately the patient turned out to be sensitive to phenobarbital and developed a rash, so that after one week this placebo was changed to one containing no active medication. One week later the blood pressure was 190/130, pulse 80. Still another week later the blood pressure was 190/120, pulse 84. After still another week on placebo therapy the blood pressure was still 190/110, pulse 80.

At that point active Rauwolfia was substituted 100 mg. morning and night. A week later the blood pressure was 165/110, pulse 64, and three weeks after this the blood pressure was 170/110, pulse 72. Since the response in blood pressure had not been as dramatic as on the first institution of the drug, veratrum (veriloid®) was added in doses of 2 mg. four times a day. Two weeks later the blood pressure was 160/90, pulse 64 and he was advised to continue. However, after six weeks the blood pressure had not shown any further change but was still 155/90 but the pulse was 56. Nevertheless he was advised to continue.

During the next two months the blood pressure ranged from 135-170/90, pulse 68; consequently veriloid was increased to 3 mg. four times a day. Six weeks later there was no further change in the blood pressure and it was decided to add small doses of hydralazine, 25 mg., four times a day. This initially failed to have any significant further effect on the blood pressure which remained at about 170/90, until the dosage of hydralazine was raised to a total of 300 mg. a day. Within a month the blood pressure fell essentially to a normal level of 140/80, pulse 84. Therefore, Rauwolfia (as rauwiloid) and veriloid were given in combination, one tablet four times a day, with apresoline® in a dosage of 100, 50, 50 and 100 mg. on a four-dose schedule. The blood pressure further moderated to 135/75. This medication was maintained and during the next four months the blood pressure fluctuated somewhat but averaged 145/85, pulse 70. He is now taking a total of 300 mg. of hydralazine, 4 mg. of rauwiloid, and 12 mg. of veriloid a day.

This case illustrates a moderately severe hypertensive male in whom the initial response to Rauwolfia was adequate on this medication alone. However, when the patient lapsed the treatment, the blood pressure returned and on reinstituting the same medication there was some beneficial effect but not a return to a normal level. Only when Rauwolfia was supplemented by veratrum and hydralazine did the blood pressure finally return to normal. The patient now will be maintained on this schedule for a number of months, and then an effort will be made to reduce the dosages, first of veratrum and next of hydralazine, and finally possibly to omit them altogether from the schedule, continuing only Rauwolfia.

Case III. A. B., a forty-five year old white housewife, was referred for treatment by a fellow internist to whom in turn she had been referred by her family doctor. She complained of occipital headaches for six months but hypertension had been discovered by her local physician only one month before. The blood pressure when first seen by the referring internist was 240/140. The optic fundi showed grade II vascular changes. The heart was moderately enlarged and there was a systolic murmur. The internist sent her into the hospital for study.

Her father had died of hypertension and one sister had hypertension. The mother had died of cancer of the stomach. In the hospital the patient's blood pressure ranged from 220/120 to 200/110 and on a sedation test reached a low of 140/90. The urine consistently showed a 1+ albuminuria and PSP excretion was 16 per cent in the first fifteen minutes with a total of 48 per cent in two hours. The electrocardiogram showed a left ventricular strain pattern but by x-ray the heart was normal in size and contour. Intravenous pyelograms revealed bilateral bifid renal pelves but no other abnormality. The patient was discharged on small doses of veratrum (veriloid) and given a salt-free diet. On this therapy her blood pressure moderated to about 170/100 to 180/110.

At this point she was referred to us for treatment. Blood pressure was 180–190/110, pulse 66. The eyegrounds still showed grade II hypertensive changes but no papilledema, hemorrhages, or exudates. An attempt was made to increase the dosage of veriloid, and during the ensuing five months the patient remained about the same and the blood pressure continued at about 170/100. Rauwolfia in the form of the

crude root 400 mg. a day was then prescribed in a four-dose schedule. It is interesting to note that the patient had already been taking all the veratrum that she could tolerate, and that after a week on Rauwolfia she suddenly became nauseated and vomited all day. Consequently she stopped the Rauwolfia.

One week later when she was seen again in the office her blood pressure was 140/80, pulse 56, and she was feeling very good. Because this was in the early stages of our trials of Rauwolfia, we decided that she was "sensitive" to it, and asked her to continue on veriloid alone. However, three months later her blood pressure was 180/110. She was still getting nauseous at times on veratrum and asked to try something else. Consequently after nine months of veratrum treatment it was stopped and Rauwolfia was reinstituted in a smaller dose of 200 mg. a day in four doses.

The patient reappeared one month later and when she walked into the office it was obvious that there had been a striking change. In the first place, she had gained eight pounds in weight. She smiled happily and announced, "All my funny feelings are gone, I feel wonderful! Before, I was skinny and couldn't gain weight; now I am getting nice and plump." She also said that it had taken Rauwolfia at least four days to produce any effect but from that point its action had been progressive. Her blood pressure was 160/90, pulse 64.

She was continued on the same therapy. A month later the blood pressure was 160/90. She again insisted on her marked improvement, stated that she was doing a great deal more at home, and that "everything had changed" in her life. The therapy was continued for another four months at which point she had gained twenty pounds but her blood pressure was still 170/100, pulse 64. However, she stated, "I feel wonderful, better than in five years and I've not had a single headache since I started these pills."

Rauwolfia was continued as the sole treatment. One month later blood pressure was 155/90, pulse 64, and it was decided to try hydralazine as additive treatment, while Rauwolfia was continued. During the next three months the dosage of hydralazine was slowly raised until she was taking 50 mg. four times a day. After one month of this dosage her blood pressure was 135/75, pulse 76. She stated she felt fine, that she was doing a great deal more but was "trying to be moderate." She did complain of a stuffy nose, particularly at night.

The same therapy was continued and she maintained a normal blood pressure until three months later, when, because of a "virus infection associated with *low blood pressure*," her local physician had stopped her hypotensive drugs and then had reinstituted only Rauwolfia. Her blood pressure rose to 180/100. She was advised to resume hydralazine. One month later her blood pressure was 150/90.

One month after that (two years after her original admission) she was readmitted to the hospital for checkup. The urine still showed 1+ albuminuria but there was moderate improvement in the PSP excretion test to 18 per cent in the first fifteen minutes and 59 per cent in two hours. The electrocardiogram was now perfectly normal. The eyegrounds were normal. She was discharged on the same therapy. During the ensuing year the blood pressure on Rauwolfia and hydralazine ranged between 145/70 and 160/85. She continued to increase her activities, had a great deal of company, and many social engagements and obligations.

After this year of therapy on hydralazine and Rauwolfia, the Rauwolfia was changed to reserpine in a dosage of 0.2 mg. a day. This did not cause any change in her blood pressure or clinical status. The blood pressure remained about 145/85, pulse 72 during the next six months. It was then decided to try to reduce the dosage of hydralazine. This was carried out successfully over a five months period, when it was finally omitted, without a rise but rather a further slight drop in her blood pressure to 135/80, pulse 68. She stated, "I am raring to go. I couldn't feel better."

This patient represents the chronic drug treatment of essential hypertension over a period of four years. Beginning with veratrum which was only moderately successful the schedule later included Rauwolfia (or reserpine) and hydralazine which latter drug was finally omitted without any rise in pressure. There has been extremely gratifying subjective and objective improvement.

SUMMARY AND CONCLUSIONS

Rauwolfia constitutes a distinct addition to the drug therapy of hypertension. While it is only moderately hypotensive, it fills a previously unfilled need, namely, for a mild, slowly and progressively active agent with few or no serious side effects. Also it meets much better than the ordinary sedatives the need for a sedativelike drug in this disease. Its definite relaxing, calming or tranquilizing action is most gratifying to hypertensive patients who typically are troubled by anxiety, irritability, aggressiveness and compulsiveness. Even in large doses Rauwolfia does not become narcotic and there is no evidence that patients become tolerant or addicted to its use.

At the very minimum, marked symptomatic improvement occurs in most hypertensive patients taking Rauwolfia. A sense of relaxed well being, "improvement in personality," and relief of the ordinary symptoms of headache, palpitation, fatigue and anxiety can be expected to occur in almost every patient. In addition the hypotensive action of Rauwolfia, although slow and moderate, is real, and when judged by statistical methods appears to be "significant." The bradycardia also is definite and often quite beneficial particularly in the ordinary, early labile hypertensive patient who usually has tachycardia with palpitation. It is also helpful in counteracting the tachycardia produced by hydralazine.

Perhaps the greatest usefulness of Rauwolfia is in combination with the more powerful hypotensive drugs with which it serves as an adjunct or background agent, smoothing the course and increasing the hypotensive effects of these more powerful agents. Because of this additive or synergistic effect it is possible not only to use lesser doses of the powerful agents effectively but also to make their actions more acceptable to the patient. Without Rauwolfia, hydralazine and hexamethonium are very difficult to use.

Rauwolfia is also quite useful in maintaining a normal or almost normal blood pressure in patients in whom this result has already been achieved but only by a combination of Rauwolfia with other drugs. It is quite apparent that Rauwolfia will maintain a blood pressure at a lower level in many patients in whom it is ineffective alone in achieving that level. Likewise, Rauwolfia will maintain normotension in many "prehypertensive" members of known hypertensive families, who have the typical labile neurogenic vasomotor responses characteristic of this group. Whether or not this "preventive" use of the drug is really worth while will be shown only by long-term studies. Apparently, however, it can be carried on indefinitely without harm to the patient and with considerable reassurance to a physician who believes that hypertension has an adverse influence upon the course of chronic vascular disease.

Treatment of Hypertensive Disease with Hydralazine*

Comparison of Its Action with That of Low Sodium Diet in Hospitalized Patients

Albert J. Stunkard, M.D., † Gerald H. Eurman, M.D., Morton Wachspress, M.D. and Arthur R. Wertheim, M.D.

New York, New York

'n the past five years a variety of new drugs for the treatment of hypertensive disease have been developed. One of the most widely used is hydralazine! (1-hydrazinophthalazine) which has been marketed since 1952 as apresoline.® Much interest has been aroused by the distinctive capacity of hydralazine to decrease vascular resistance selectively in the splanchnic area, an effect which has been noted particularly in the kidney where increases in blood flow of 60 per cent have been reported^{1,2} following intravenous administration of the drug. The resultant decrease in total peripheral resistance is sufficient to produce a moderate lowering of blood pressure despite an increased cardiac output^{2,3} of the order of 100 per cent.

Despite early reports^{4,5} that hydralazine was ineffective under clinical conditions, subsequent investigators^{6–10} have concurred in a cautiously optimistic view as to its usefulness, reporting that 35 to 70 per cent of hypertensive patients have experienced significant falls in blood pressure during hydralazine therapy, and a considerably smaller number have had concomitant improvement in other manifestations of hypertensive disease. Toxic and side reactions have not seriously interferred with its use. A more recent note reports the development of an arthritic syndrome following prolonged administration of hydralazine.¹¹

All of these reports on the therapy of hyper-‡ Hydralazine used in this study was generously sup-

plied by Dr. E. A. Reilly of Ciba Pharmaceutical Prod-

tensive disease with hydralazine have dealt with treatment of outpatients. This report presents a study of the effect of hydralazine in a controlled hospital population under conditions established in previous studies on the effect of low sodium diets on the hypertensive state. An opportunity was thus provided to compare the effects of such diet with hydralazine therapy, often in the same patients.

METHODS

Twenty-five patients from the wards of the Columbia University Research Service, Goldwater Memorial Hospital, are the subjects of this report. The primary diagnosis of each patient was essential hypertension, the diastolic pressure on admission being at least 110 mm. Hg. There were sixteen men in the series with an average age of fifty-six (range thirty-seven to seventy-eight) and nine women with an average age of forty-eight (range twenty-three to seventy-one). Fourteen of these patients had previously been treated with a 95 mg. sodium diet during hospitalization on the Service.

On admission the following tests were performed: history and physical examination, record of early morning blood pressures, fundus examination by an ophthalmologist, 6-foot chest film for heart size, intravenous pyelogram, electrocardiogram, complete blood count, erythrocyte sedimentation rate, urinalysis, blood urea nitrogen, fasting blood sugar, PSP excretion, cold pressor and intravenous benzodioxane and/or regitine.® With the exception of the

and/or regitine.® With the exception of the *From the Research Service, First (Columbia University) Division, Goldwater Memorial Hospital, Department of Hospitals, New York City, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y. This study was supported in part by grants from the National Institutes of Health and the Albert and Mary Lasker Foundation.

† Present address: Department of Medicine, Cornell University Medical College, New York, N. Y.

intravenous pyelogram and the tests for pheochromocytoma, all procedures were repeated at the conclusion of the control period and again at the end of the treatment period. The basal metabolic rate was determined during the control and treatment periods in eight patients.

The control period was of sufficient duration to establish a stable blood pressure level, and averaged eight weeks in duration (range four to twelve weeks). During this and the subsequent treatment period all patients were ambulatory and participated in the relatively constant program of ward activities. Except for one patient, J. P., on a house diet they were maintained throughout the study period on a diet containing 1.5 gm. of NaCl per day.

Oral test doses of hydralazine given prior to therapy showed a maximum response within three hours and no prolonged effect. Accordingly, the drug was administered at four-hour intervals from 6 A.M. to 10 P.M., the last dose being omitted if the patient were already asleep. The initial oral dose was either 10 or 25 mg., and this was increased by increments of 10 to 25 mg. until blood pressure response was achieved or side effects limited dosage. The average daily dose was 530 mg. (range 250 to 1,000 mg.).

Early morning blood pressures were measured as described in previous publications from this Service. 12,13 Determinations were made by physicians with a mercury sphygmomanometer three times weekly while the patient was lying in bed before more than minimal daily activity had been undertaken. During the treatment period these early morning blood pressures were taken an average of two hours after the first dose of drug. Three readings were made, and the lowest systolic and diastolic pressures were designated as the early morning pressure for the day. The three early morning pressures in each week were averaged and considered the blood pressure level for that week.

In presentation of the data, blood pressure values are reported under three categories: The "control" pressure is the average of the three weekly pressures before the start of the treatment period, and thus is derived from twenty-seven readings obtained under comparable conditions. Similarly, the "final response" is the average of the last three weeks of the treatment period. A "maximal response" is presented as the lowest weekly average following an increased dose of drug and, in contrast to the two previous measures, is derived

from only nine blood pressure readings. The average duration of the treatment period for the twenty-three patients who were able to tolerate the drug at least three weeks was twelve weeks (range three to twenty-five weeks). In two cases toxic reactions forced treatment to be discontinued within a week.

RESULTS

Effects of Hydralazine on Blood Pressure

Prolonged Oral Administration. Table 1 summarizes the data on blood pressure levels during the control, "maximal response" and "final response" periods. The mean diastolic values for these twenty-three patients were: control 111 mm. Hg, maximal response 92, final response 97, representing a mean fall of 19 mm. Hg for the maximal response and 14 mm. Hg for the final period. As will be noted from Table 1, twenty-two of the twenty-three patients who were able to take the drug for at least three weeks showed a maximal response greater than 10 mm. Hg diastolic. However, the final response of only seventeen of these twenty-three subjects was greater than 10 mm. Hg. When the blood pressures of the control and final response periods were analyzed by means of the "t" test, it was found that significance of P < 0.01 could be ascribed to the changes ranging from 16 to 31 mm. Hg which occurred in ten patients. In seven additional patients whose fall was 11 to 16 mm. Hg, significance of P < 0.05 was found. These seventeen patients were considered responders to hydralazine therapy.

Figure 1 illustrates a case with a maximal response to hydralazine which is both significant and maintained throughout the treatment period. When hydralazine was discontinued after thirteen weeks the blood pressure returned to pretreatment levels within three weeks.

In an effort to determine the relationship of the early morning blood pressures to fluctuations during the day, random blood pressure determinations were made repeatedly in eight patients in the supine position and compared with the corresponding early morning blood pressure during both the control and treatment periods. During the control period the diastolic pressures taken during the day averaged 13 mm. Hg (range four to twenty-three mm. Hg) higher than the early morning pressures, while during the treatment period the random pressures were 9 mm. Hg higher (range 0 to 24 mm. Hg). This

TABLE I

Patient Age Sex	Response to Diet	Blood Pressure			Change in Blood Pressure		Dura-		
		Control	Maximal Response	Final Response	Control vs. Final Response	Proba- bility	tion Rx (wk.)	Toxic Effects	Remarks
Responders: J. W., 56, M	0	244/145	213/113	244/114	-20/-31	<0.01	11		Hematuria stopped bu PSP excretion fell from 40 to 20% in 2 hr.; hgb 14.6 to 13 gm.
G. C., 27, F		193/126	165/ 95	161/ 97	-32/-29	<0.01	9		Cardiac failure de-
R. C., 51, M	+	209/135	182/106	182/109	-27/-26	<0.01	21	Severe headaches	creased; fundi improved Marked decrease cardiac failure, fundi improved BUN 26→8 mg. %. hgb. 15 to 12.9 gm.
M. H., 71, F M. S., 37, M	+	193/103 189/121	159/ 82 163/ 95	156/ 84 169/102	-37/-19 -20/-19	<0.01 <0.01	4 18		Hgb. 13 to 11 gm. Decreased weakness; increased feeling of well being; heart size decreased; congestive failure decreased; hgb 16.5 to 15.1 gm.
H. C. 23, F J. B., 59, M	**	171/ 99 179/119	142/ 75 158/101	154/ 80 155/101	-17/-19 $-24/-18$	<0.01	14 13	Headaches	PSP excretion 25 → 45 %
C. B., 65, M C. K., 56, F	0	207/118	176/ 98 172/ 87	192/102	-15/-16 $-19/-15$	<0.02	12	Headaches; nausea and vomiting; palpitations	Fundi improved; hear
J. P., 43, M	+	212/114	189/ 89	187/100	-25/-14	<0.05	9	Myocardial infarction; headaches	
A. A., 78, M B. F., 52, F S. R., 37, F	++++	187/100 190/100 182/110	175/ 79 191/ 86 177/ 99	173/ 86 189/ 88 179/ 99	-14/-14 - 1/-12 - 3/-11	<0.01 <0.01 <0.01	12 13 15	Headaches; nausea and vomiting; "hysterical stupor"; palpitations	
M. J., 52, F E. B., 76, M	0	167/104 216/100	142/ 79 192/ 84	160/ 93 195/ 89	- 7/-11 -21/-11	<0.02 <0.05	25 3	Psychosis Vertigo causing cessation of treatment	Tolerance
W. M., 64, M M. B., 54, M		187/ 96 169/122	177/ 82 169/103	171/ 84 163/112	-16/-11 - 6/-10	<0.05 <0.05	3 23	Headaches	Heart size decreased; tolerance
Non-responders: L. S., 56, M	0	235/115	205/ 98	218/107	-17/- 8		14	Headaches	Nitrogen retention Only two pa- tients with BUN
L. M., 39, M	0	203/125	195/111	202/120	- 1/- 5		16		Nitrogen retention > 50 mg.
A. M., 48, F R. O., 54, M	0	202/106 186/100	196/ 86 174/ 86	199/102 187/ 91	- 3/- 4 + 1/- 9		13 10	Nausea and vomiting Dose limited by headaches	
E. L., 63, F	+	171/ 94	158/ 82	179/ 89	+ 8/- 5		9	Dose limited by vertigo	
	1	1	1	Discontinu	ed Because of U	Untoward R	Reactions		
W. R., 50, M		179/102	165/ 97	172/103	- 7/+ 1	••••	3		Discontinued because of severe headaches; at this time EKG showed evidence of increased myocardial damage, and there was increased
J. M., 49, M	••	154/ 96	• • • • • •				1		congestive failure Development of severe drug fever in first week of treatment; patient had multiple sclerosis
B. D., 69, M		198/104			*******		1 day		Cerebral vascular acci- dent day after starting hydralazine; three pre- vious ones
E. B., See	above.			******					

was taken as evidence that the early morning blood pressures in both control and treatment periods adequately reflected changes occurring during the rest of the day.

Response to Intravenous Test Doses of Hydralazine. In the early part of the study intravenous test doses of hydralazine were given to sixteen pa-

tered during oral maintenance. For this reason, as well as its limited usefulness in predicting responders to oral medication, this method of selecting patients was abandoned before completion of the study.

Tolerance to the Effects of Oral Hydralazine. Tolerance, as here employed, signifies that more

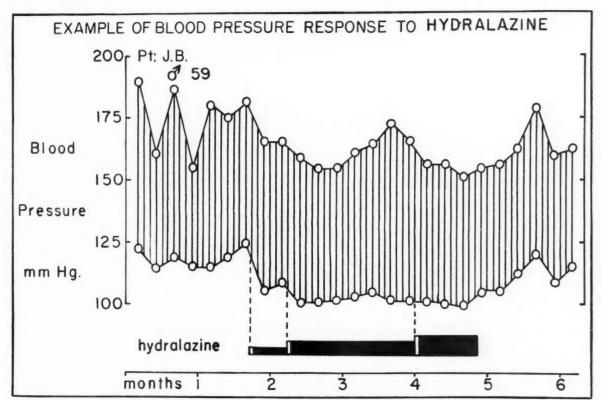


Fig. 1. Patient J. B. with a blood pressure of 179/119 in the control period shows a "maximal response" of 158/101 and a "final response" of 155/101. When hydralazine was discontinued, blood pressure returned to pretreatment levels.

tients during the control period to see if subsequent response to oral administration could be predicted. An initial dose of 10 mg. was administered over a two-minute period to patients in a resting condition; if there was no hypotensive response, on subsequent days the dose was increased by 5 mg. to a maximum of 20 mg. A diastolic blood pressure fall of greater than 10 mm. Hg was noted in fourteen patients, of whom ten later responded to oral medication and four did not. The two patients, R. C. and C. B., who did not respond to intravenous hydralazine were unable to tolerate more than 10 mg. because of severe side reactions but by careful management achieved oral doses of 500 and 800 mg. per day which resulted in significant blood pressure decreases. Side reactions following intravenous hydralazine tended to be more common and severe than those encounand more of a drug must be used to produce equivalent effects. ¹⁴ The development of tolerance to the hypotensive effects of hydralazine has been previously reported ^{7,9} and denied. ^{8,10} In the present series two patients, M. J. and M. B., were observed whose response to hydralazine indicated development of tolerance to the drug. The course of patient M. J. is illustrated in Figure 2. It will be noted that gradually increasing doses of hydralazine were required to reproduce the hypotensive effect first obtained with 75 mg. of the drug.

Effects of Hydralazine on Other Manifestations of Hypertensive Disease

Investigation of hydralazine was not confined to its effects on blood pressure but included also its influence on such other manifestations of hypertensive disease as signs and symptoms, hypertensive retinopathy, cardiomegaly and electrocardiographic abnormalities. Favorable changes in these categories were found in only a small percentage of patients with a blood pressure response to hydralazine.

Signs and Symptoms. Of a total of ten patients with symptoms of congestive failure, improve-

and from grade III to grade II in three others, C. B., R. C. and S. R. Deterioration of eye-grounds during the treatment period did not occur.

Heart Size. At the end of the control period the cardiac silhouette was enlarged in fifteen patients, of whom ten were in congestive failure.

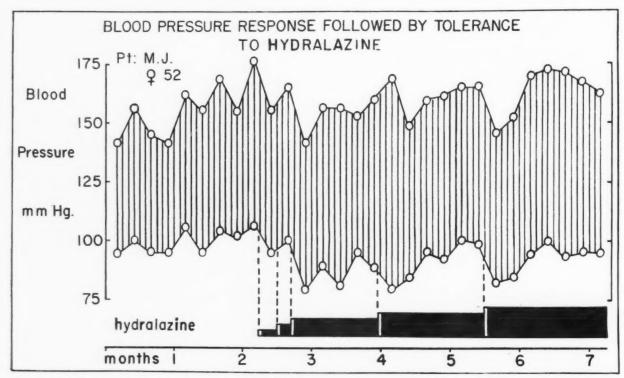


Fig. 2. Patient M. J. with a blood pressure of 167/104 in the control period shows a "maximal response" of 142/79. Development of tolerance at three increasing dosage levels is illustrated, resulting in a "final response" of 160/93, a fall of only -7/-11.

ment occurred in four: M. S., R. C., G. C. and B. F. Each experienced a decrease in dyspnea together with a diminution in objective evidence of congestive failure. Anorexia and nausea associated with failure was decreased in two of these, M. S. and R. C. In one patient, R. C., it was possible to reduce the daily dose of digoxin from 0.5 to 0.25 mg. Headaches were greatly improved in two of the four patients (G. C. and S. R.) with this symptom.

Hypertensive Retionopathy. Examinations of the optic fundi of eighteen patients were performed by an ophthalmologist at the conclusion of the control and treatment periods. Grading was according to the Keith-Wagener-Barker scale 15 in which grades I and II refer to vessel caliber; grade III includes superimposed exudates and hemorrhages; grade IV is characterized by the presence of papilledema. A change from grade IV to grade II was observed in one patient, G. C.,

Only three of these, M. B., C. B. and M. S., showed a decrease of more than 1 cm. in transverse diameter at the end of the treatment period. A further increase in heart size was not observed in any of the patients.

Basal Metabolic Rate. A report¹⁶ that intravenous administration of hydralazine to dogs resulted in a 30 per cent increase in oxygen consumption prompted determinations of the basal metabolic rate in eight patients during the control and treatment periods. A significant change was not observed in any of these subjects.

Erythrocyte Count. The chemical similarity of hydralazine to phenylhydrazine has aroused speculation as to its possible effects upon the hematopoietic system. No such adverse effects have been reported to date. However, in the present study small but significant degrees of anemia developed in four patients during treatment with hydralazine. The anemia was of the

normochromic, normocytic type, with an average fall in hemoglobin of 1.8 gm. and in hematocrit of 6 per cent. The presence of renal failure sufficient to result in nitrogen retention may have contributed to this finding in one of the patients, J. W. No explanation for the anemia was apparent in the other three patients, M. H., M. S. and R. C.

Renal Function. The routine clinical tests of renal function revealed no significant changes during hydralazine therapy in twenty patients. In one patient, J. W., treatment was accompanied by markedly reduced hematuria and albuminuria, while PSP excretion fell from 40 to 20 per cent. In a second patient, J. B., there was an increase in PSP excretion and in a third, R. C., a decrease in blood urea nitrogen levels.

Untoward Reactions during Hydralazine Therapy

Headache. Untoward reactions during hydralazine therapy have been reported by all authors and were observed in this study. As will be seen from Table II, by far the most common such reaction was headache which occurred in nine patients. This was almost always of a throbbing type and was often associated with flushing of the face. It was most commonly generalized, sometimes frontal and/or occipital in location. Intensity of the pain was mild to moderately severe and it was usually relieved partially by aspirin and completely by demerol.® Response to antihistamines (pyribenzamine®) was inconstant. The headaches appeared just after the institution of hydralazine or after an increase in dose, and began most often in the early morning and lasted from an hour to all day. They tended to decrease in intensity and disappear within a week. Headache forced discontinuation of therapy in only one patient, W. R., although it limited the dose of hydralazine in one other, R. O.

Of the seventeen patients who received intravenous test doses of hydralazine six complained of a headache which was of the same type as observed on oral administration. Headache occurred either within half an hour after the injection or about six hours later. The former was correlated with a fall in blood pressure; the latter with a subsequent rise to hypertensive levels.

Myocardial Damage. The ability of hydralazine to produce tachycardia and increased cardiac output suggests that its administration may be dangerous in the case of a heart already under

strain. On the other hand, the beneficial effects of dietary and surgical treatment on electrocardiographic abnormalities of hypertensive patients suggest the possibility that this may be a non-specific effect of blood pressure lowering, and thus to be expected also from drug therapy.

Table II
UNTOWARD REACTIONS DURING HYDRALAZINE THERAPY
IN TWENTY-FIVE PATIENTS

Reactions	Occur- rence	Necessitating Cessation of Treatment	Occurrence in I.V. Test (16 patients)	
Headache	9	1 (caused dose to be limited in 2 others)		
Nausea and vomiting	3	0	3	
Dizziness	2	1 (caused dose to be limited in 1)	0	
Emotional disturbance	2	0	0	
Myocardial damage	2	0	1	
Fever	1	1		
Cerebral vascular accident	1	1		
Palpitations	2	0	1	
Postural hypotension	0	0	3	

The first reports^{8,9} to consider this problem as it relates to hydralazine therapy have indicated that cardiac status does not improve and that incidence of electrocardiographic abnormalities is increased. Accordingly this problem was studied with the aid of electrocardiograms before and during treatment in twenty-one patients in this series.

Evidence of myocardial damage was found in two patients during drug treatment. One, W. R., was a fifty year old man with previous myocardial damage who went into more severe congestive failure in his first week on hydralazine. Electrocardiograms showed that T₂ had become inverted, the P waves flattened and that numerous auricular and ventricular premature contractions had appeared. The second patient, J. P., a forty-three year old man with a normal electrocardiogram, developed a classic myocardial infarction during his eighth week of treatment at a time when blood pressure had fallen from 212/114 to 187/100 and he was asymptomatic.

In addition to these two patients, a fifty-six year old woman with a past history of fourteen years of hypertension, myocardial infarction and angina responded unfavorably to an intravenous test with hydralazine. Twenty minutes after receiving 10 mg. of the drug, and following a fall in blood pressure from 206/118 to 174/98, she developed severe pain in the left side of the

chest posteriorly. Subsequent electrocardiograms showed that T_2 had become depressed and T_3 and $VT_{3,4,5}$ inverted. Over a period of six weeks all these changes except the inverted VT_4 returned to normal and it seemed likely that she had sustained a small myocardial infarction.

TABLE III
RESPONSE TO RICE DIET AND TO HYDRALAZINE TREATMENT
OF PATIENTS WITH HYPERTENSIVE DISEASE

OF PATIENT	s WITH	HYPERT	TENSIVE	DISEASE	
	Blood Pres- sure	Fundi	Heart Size	EKG	Car- diac Fail- ure
	Ri	ce Diet		1	
Total patients	50	36	33	28	17
Improved	36	13	19	9	9
Unchanged	14	26	14	18	8
Worse	0	0	.0	1	0
	Нуа	dralazine			
Total patients	25	18	15	21	10
Improved	17	4	3	1	4
Unchanged	8	14	12	18	5
Worse	0	0	0	2	1

Cerebral Vascular Accident. One sixty-nine year old man, B. D., with a past history of three cerebral vascular accidents suffered a hemiplegia the day after starting hydralazine. As in his previous episodes there was recovery with minor residua in a period of ten days, and the relationship to hydralazine administration was not established.

Fever. In one patient, J. M., who was suffering also from multiple sclerosis with evidence of brain damage, fever to 105°F. occurred at the end of the first week of treatment, forcing its termination. Test doses of hydralazine on two occasions soon thereafter resulted in a recurrence of fever for which no other cause was found. Similar doses a year later were well tolerated.

Emotional Disturbances. Psychosis following hydralazine has been reported only once¹⁷ prior to this study in which unusual emotional disturbances were observed in two patients. In one, S. R., an acute hysterical stupor appeared in the sixth week of treatment, cleared three days after medication was stopped and did not recur upon

its readministration. In the other, M. J., a woman of fifty-two with brain damage from two previous hemiplegias, primitivization of behavior began in the third month on hydralazine, continued with little change for three months and cleared promptly upon cessation of treatment.

Nausea and Vomiting. Nausea and vomiting occurred in three patients on oral medication and in three receiving intravenous tests, indicating that gastric irritation was not the sole factor in its production. These symptoms were never severe nor did they limit treatment.

Vertigo. Both of the patients who complained of dizziness from hydralazine had a past history of Ménière's syndrome and similar complaints occurred during both the control period and following treatment. Postural hypotension was not associated with this dizziness. Nevertheless the symptoms were more severe than usual during the medication period and it became necessary to terminate treatment in one patient, E. B., for this reason.

Postural Hypotension. Postural hypotension, which has been reported during prolonged oral administration of hydralazine, was rarely observed in this study, even after oral doses which resulted in lowering of the blood pressure in the supine position. However, three of the patients, who received intravenous test doses with marked fall in blood pressure, were found to have postural hypotension without apparently associated symptoms.

COMPARISON WITH TREATMENT BY LOW SODIUM DIETS

An opportunity for evaluating the therapeutic effectiveness of hydralazine in hypertensive disease is provided by comparison of its effects with those obtained on this Service by severe dietary restriction of sodium. Both the latter 12,13 and the present studies were carried out under the same conditions, using identical methods and similar patient populations. Furthermore, fourteen of the patients in the present report had previously been treated on this Service with a low sodium diet. The results of treatment with rice diet and with hydralazine are summarized in Table III.

It can be seen that diastolic blood pressure decreases of at least 10 mm. Hg were obtained in thirty-six of fifty patients (72 per cent) on the rice diet as compared with seventeen of twenty-five who received hydralazine (68 per cent). In

neither series was there a significant elevation of blood pressure during treatment.

Fourteen patients in the present series had been treated previously with a low sodium diet. Seven had shown a significant blood pressure decrease and seven had not; this group therefore included a larger number of dietary non-responders than the rice diet series as a whole. Nevertheless, after return to the control diet ten of these fourteen subjects showed a significant blood pressure response to hydralazine. Of the seven dietary responders six responded to hydralazine; of the seven dietary non-responders four responded to hydralazine. It is clear that failure of dietary treatment does not preclude effective hydralazine therapy.

Decrease in transverse cardiac diameter of more than 1 cm. was observed in nineeten of thirty-three patients on the rice diet as compared with three of fifteen on hydralazine. Similarly, improvement in hypertensive retinopathy of at least one grade according to the Keith-Wagener-Barker scale occurred in thirteen of thirty-six patients on the rice diet and in only four of eighteen receiving the drug. There was no deterioration in these indices of hypertensive disease during treatment by either method. A greater efficacy of diet in the management of congestive failure is possibly manifested by the finding that nine of seventeen patients improved on this regimen as compared with four of ten on hydralazine.

The most striking difference between the dietary and hydralazine treatments was noted in their effects upon the electrocardiogram. The rice diet produced electrocardiographic improvement in nine of twenty-eight patients, with deterioration (due to myocardial infarction) appearing in only one. In contrast, improvement was noted in only one of twenty-one patients on hydralazine and deterioration in two.

Serious complications of therapy were uncommon in both series, each of which contained one myocardial infarction and one cerebral vascular accident, none definitely attributable to the treatment. Minor complaints were present in the rice diet series and tended to be more troublesome than those described with hydralazine. Thus there was a "general unhappiness about the stringent deprivations" of the diet, together with lassitude and weakness in 30 per cent of the patients. Another 30 per cent of the patients required modification of the diet due to severe gastrointestinal complaints. The addition

of liberal amounts of protein, fat and vegetables of low sodium content significantly reduced side reactions to the rice diet without diminishing its therapeutic effect. ¹² However, these modifications did not greatly increase the palatability of the diet and required even more extensive dietetic supervision.

COMMENTS

The evaluation of any current treatment for hypertensive disease faces difficulties which arise not only from the non-specific nature of the treatment but also from the long and variable course of the disease. 18,19 Two questions are raised: first, can blood pressure be lowered over a long period of time and, second, does such a lowered blood pressure influence the course of the disease? The present study is an effort to answer the first question, whether hydralazine meets the criteria of safety, effectiveness and convenience required for widespread and prolonged use. Only such an agent will allow the duration of treatment necessary to determine its effect on the course of the disease. Evidence already available suggests that lowering blood pressure has a favorable effect on this course since a variety of surgical, dietary and pharmacologic treatments with apparently little in common except their anti-hypertensive effect have led to regression in other manifestations of hypertensive disease.

Previous studies from this Service^{12,13} have established in some detail the rigorous criteria which must be met before changes in hypertensive disease occurring during a therapeutic regimen can be considered either specific or significant. Such changes are most readily evaluated in hospitalized patients maintained on a constant level of activity and a constant diet. The effects of hospitalization itself must be controlled by a sufficiently long period of observation to ensure stabilization of the disease process in general and of the early morning blood pressures in particular. This has required as long as twelve weeks, and it was necessary to exclude several patients from the present study because of the difficulty in obtaining an adequate

Daily observation of the patient under these conditions allows for a precision of observation which is hardly possible under other circumstances. Stability of the blood pressure averages, for example, is such that a significance of p < 0.05 may be attributed to diastolic responses of

greater than 10 mm. Hg, and significance of p < 0.01 to diastolic responses of greater than 16 mm.

Evaluation of the therapeutic effect of hydralazine may be facilitated by comparison with the results obtained with low sodium diets. The only previous such comparison is that of Gill et al.20 who have reported on seven patients treated at different times with dietary restriction of sodium and again with hydralazine. One of these patients responded to both regimens and one to sodium restriction but not to hydralazine. In the series reported here, in which a considerably larger percentage responded to each regimen, it would appear that diet is somewhat more effective than hydralazine. Thus while about 70 per cent of patients treated under comparable conditions with each method had a significant fall in diastolic blood pressure, a higher percentage of those treated with diet showed improvement in hypertensive retinopathy, cardiac enlargement and electrocardiogram. The significance of this improvement in the electrocardiogram of those on diet is unclear in view of recent work²¹ suggesting that this may be an artefact based on an altered electrolyte pattern.

In terms of ease of management, hydralazine treatment has many advantages over low sodium diets. The anti-hypertensive effect is more rapidly achieved and is less readily jeopardized by a break in the regimen. Troublesome side reactions are less common than on the rice diet and not more frequent than are found on the modified low sodium diet. Such modifications do not, however, greatly increase palatability and even these diets were less acceptable to the patients than hydralazine therapy. Finally, drug treatment obviates the considerable investment in a special kitchen and the extensive dietetic supervision which have been found necessary for effective inpatient treatment with diet.

The results of the present study indicate that hydralazine has an effect on blood pressure comparable to that of low sodium diets without achieving the same degree of improvement in such other manifestations of hypertensive disease as retinopathy, cardiac enlargement and electrocardiographic abnormalities. It can be administered with relative safety and is better accepted by patients than is dietary treatment. It appears suitable for use in the long-term studies which alone can determine whether drug therapy may affect the natural history of hypertensive disease.

CONCLUSIONS

1. A controlled study of the effects of hydralazine in the hospital treatment of twenty-five patients with essential hypertension is reported. These results are compared with those obtained under the same conditions by treatment with low sodium diets.

2. Significant reduction in blood pressure was achieved in seventeen patients (68 per cent) over an average of thirteen weeks. There was regression of such changes as hypertensive retinopathy and cardiac failure in less than 25 per

cent of these patients.

3. Side reactions in most, and tolerance in some patients, require careful regulation of dosage and supportive measures. The duration of this study does not permit conclusions as to possible ill effects of prolonged administration of hydralazine.

4. Hydralazine probably should not be used in patients with evidence of coronary or cerebral artery disease. This appears to be the main defi-

nite contraindication.

5. Comparison with treatment by low sodium diet reveals hydralazine to be of some what lesser therapeutic potency. This disadvanta e may be compensated by the greater ease of ma prement of the drug.

REFERENCES

 Reubi, F. Influence de quelques vasodilateurs périphériques sur le flux sanguin renal. Helvet. med. acta, 16: 297, 1949.

 WILKINSON, E. L., BACKMAN, H. and HECHT, H. H. Cardiovascular and renal adjustments to a hypotensive agent. J. Clin. Investigation, 31: 872, 1952.

 SCHMID, A. and REUBI, F. Hämodynamische Eigenschaften zweierneuer Phthalazinderivate. Helvet.

med. acta, 17: 543, 1950.
GRIMSON, K. S., CHITTUM, J. R. and METCALF, B. H. Actions of 1-hydrazinophthalazine (C-5968) on vasomotor reflexes and hypertension in dogs and

man. Federation Proc., 9: 279, 1950.

 MOYER, J. H. and HANDLEY, C. A. Renal function and systemic blood pressure changes following the administration of hydrazinophthalazine. J. Lab. & Clin. Med., 36: 969, 1950.

- RIVEN, S. S., POCOCK, D. G., KORY, R. C., ROEHM, D. C., ANDERSON, R. S. and MENEELY, G. R. The control of hypertension with 1-hydrazinophthalazine (apresoline). Am. J. Med., 14: 160, 1953
- Schroeder, H. A. The effect of 1-hydrazinophthalazine in hypertension. *Circulation*, 5: 28, 1952.
- TAYLOR, R. D., DUSTAN, H. P., CORCORAN, A. C. and PAGE, I. H. Evaluation of 1-hydrazino-phthalazine (apresoline) in treatment of hypertensive disease. Arch. Int. Med., 90: 734, 1952.

- 9. Moyer, J. H. Hydralazine (Apresoline®) hydrochloride, pharmacological observations and clinical results in the therapy of hypertension. *Arch. Int. Med.*, 91: 419, 1953.
- HAFKENSCHIEL, J. H. and LINDAUER, M. A. 1-hydrazinophthalazine (apresoline) in the treatment of hypertension: a two-year study. *Circulation*, 7: 52, 1953.
- Dustan, H. P., Taylor, R. D., Corcoran, A. C. and Page, I. H. A syndrome elicited by prolonged administration of large doses of hydralazine. J. Lab. & Clin. Med., 42: 801, 1953.
- 12. WATKIN, D. W., FROEB, H. F., HATCH, F. T. and GUTMAN, A. B. Effects of diet in essential hypertension. I. Baseline study: effects in eighty-six cases of prolonged hospitalization on regular hospital diet. II. Results with unmodified Kempner rice diet in fifty hospitalized patients. Am. J. Med., 9: 428, 1950.
- HATCH, F. T., WERTHEIM, A. R., EURMAN, G. H., FROEB, H. F., WATKIN, D. M. and EPSTEIN, H. A. Effects of diet in essential hypertension. III. Alterations in sodium chloride, protein and fat intake. Am. J. Med., 17: 499, 1954.
- 14. TATUM, A. L., SEEVERS, M. H. and COLLINS, K. H. Morphine addiction and its physiological inter-

- pretation based on experimental evidences. J. Pharmacol. & Exper. Therap., 36: 447, 1929.
- KEITH, N. M., WAGENER, H. P. and BARKER, N. W. Some different types of essential hypertension; their course and prognosis. Am. J. M. Sc., 197: 332, 1939
- 16. Marks, P. A. and Reynele, P. C. Abstract. J. Clin. Investigation, 32: 586, 1953.
- Moser, M., Syner, J., Melitz, S. and Mattingly, T. W. Acute psychosis as a complication of hydralazine therapy in essential hypertension. J. A. M. A., 152: 1329, 1953.
- Blood, D. W. and Perera, G. A. Hypertensive vascular disease (duration of life in a selected series). Am. J. Med., 4: 83, 1948.
- Perera, G. A. Diagnosis and natural history of hypertensive vascular disease. Am. J. Med., 4: 416, 1948
- GILL, R. J., DUNCAN, G. C. and REINHARDT, D. J. Arterial hypertension: the therapeutic effect of sodium restriction combined with 1-hydrazinophthalazine or dibenzyline. Am. J. M. Sc., 226: 249, 1953.
- 21. Kohn, R. M. and Kiley, J. E. Electrocardiographic changes during hemodialysis with observations on contribution of electrolyte disturbance to digitalis toxicity. *Ann. Int. Med.*, 39: 38, 1953.

Conference on Therapy

How to Evaluate a New Drug

THESE are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

Dr. Harry Gold: The problem of clinical evaluation of new drugs at the present time presents a serious bottleneck to therapeutic progress. The laboratories are bursting at the seams with new chemical agents relating to almost every field of treatment. There are the large numbers of local anesthetics, general anesthetics, adrenergic and cholinergic compounds, the peripheral blocking agents, central nervous stimulants and depressants, cardiac agents, diuretics and others. The pharmacologic laboratories are doing a very good job in screening these materials but there is always the need of getting the final answer from clinical pharmacology, studies made directly in human subjects. Here is where the advance slows down

Three needs are in evidence here, physicians familiar with the management and sufficiently trained in scientific investigative procedures; sufficient clinical facilities suitably organized for this purpose; and the development of good methods for testing drugs, comparing one agent with another in such a way as to secure the most information with the fewest number of patients in the shortest possible time. These are the problems but in this conference we are going to explore only one of them, namely, methods for clinical evaluation of a drug, how to do this in human subjects in such a way as to obtain a verdict not likely to be reversed. If we are not going to do a particular study ourselves, the results of this conference should help us to see what we have to look for in the reports of others, for one can get a very good notion about the validity of conclusions from the kind of methods that were employed. Dr. William Grace will lead off the discussion.

DR. WILLIAM J. GRACE: It is well known that the response to a particular pharmacologic agent in a group of patients is not invariably the

same or even predictable. When we learn that a certain agent proved effective in, say 35 per cent of the patients, we accept the result and let it go at that. This is one way of evaluating a therapeutic agent. There are other questions which need to be raised and answered and I will confine my comments to some of the experiments that we have recently made in this connection. I refer to the matter of determining the factors in any particular individual which alter the responses to the drug in question from time to time. It helps to understand why an agent may fail to work at one time or produce more effect than anticipated at another.

We have had opportunity to make a variety of observations on the responses of the gastrointestinal tract during various mood and feeling states in our subject, Tom, a man with a gastric fistula. In one instance, he was lying on the table and carrying on a free discussion of appetizing foods which appealed to him. This was late in the morning, he felt hungry, and expressed the desire to eat. At this time the stomach showed an increase in blood flow, total acid secretion and gastric motility. Under these circumstances the introduction of beef bouillon into the stomach was followed by further increase in blood flow and secretory and motor activity. The result was different when the same experiment was made at a time when the subject felt discouraged and depressed, preoccupied with self-criticism because of his inability to effectuate a deal in the purchase of a house. During this period he complained of fullness after eating, lack of appetite and loss of interest in eating. At this time the same beef bouillon stimulus was followed by little or no change in the secretion or motor activity of the stomach.

Changes in stomach function during anger were observed in this subject. Tom was discussing his attitude toward a man who had recently discharged him from his employment under circumstances which the subject felt were embarrassing and humiliating. He showed visible anger. In this state the stomach showed an increase in blood flow, hydrochloric acid and motility.

During fear the opposite was noted. Tom was suddenly faced with the fact that his supervisor would soon become aware of Tom's lack of attention to carrying out the jobs that he had been assigned. The professor entered the laboratory and searched for a protocol book which Tom was thought to have filed. Tom became frightened that his laxity would be discovered and he would be discharged. However, the professor found the book and walked out satisfied. Sharp changes in the behavior of the stomach took place. During the sudden experience of great fear there was blanching of the mucosa, decline of secretion and cessation of motor activity. During the period of recovery of confidence the blood flow increased and motor activity rapidly returned. Such changes in either direction occur rapidly without the individual necessarily verbalizing any feeling state that may be associated with them. In the laboratory, changes often appeared in the stomach before the particular drug was introduced. The nature of the change depended on his attitude at the time. For example, when Tom was frightened by the prospect of taking a large and disagreeable looking pill, his stomach became pale and hypoactive before the medicament was administered. On another occasion Tom became angry at being given an injection. Hyperfunction of the stomach was noted before the injection.

When the subject ate an average meal at a time when he felt hungry and was interested in eating, the gastrocolic reflex was brisk, resulting in increased blood flow, motor activity and secretory activity in the large bowel. It was not brisk, however, when the food was introduced directly into the patient's stomach or when he forced himself to eat without much appetite. Under these circumstances none of the changes indicating activity of the gastrocolic reflex took place.

An attempt has been made to get around the difficulty of persons reacting differently to different laboratory situations by making use of a standard type of stress stimulus. This has not proved very successful, since different persons exposed to the same trying circumstances react in different ways to it. In one group of experi-

ments, observations on the large bowel were made while the subjects were exposed to the stressful situation of having a tight metal band clamped around their head. In one subject the bowel became very pale and hypomotile during the period of the intense pain; this man later reported that he had been overcome with feelings of intense fear and fright. In another subject the same situation caused an increase in the blood flow and an increase in the motor activity of the large bowel, this person reporting that he was not frightened by it at all but was in a state of conflict over his wish to go ahead with the experiment and angry feelings at us for subjecting him to such an uncomfortable procedure.

The effect of a drug differs with the patient's mood at the time it is given. When our subject Tom was angry, the stomach showing high color, high acid secretion and hyperfunction, a dose of 0.6 mg. atropine failed to alter the motility or secretion. On another occasion when he was feeling more calm and secure and cheerful in his attitude toward us, the same dose of atropine was followed by cessation of motor activity in the stomach. Similarly in the colon, on a day when afistulous, he was clearly preoccupied with thoughts that he was being treated as a freak, was embarrassed and humiliated by the procedures and wished he had never gotten involved in them, an injection of 2 mg. of atropine intravenously was followed by no significant change in blood flow, secretory or motor activity of the bowel. At a later date during a time when he was feeling very much more cheerful and kindly disposed toward the experiment and laboratory procedures, the same dose of atropine resulted in marked hypofunction of the colon.

What I have pointed out here applies not only to atropine but also to the effect of food and other drugs such as physostigmine, prostigmine, acetylcholine and histamine. These experiments all go to show that in evaluating a drug one needs to know not only the nature of the drug and the dose but also the status of the individual at the time the drug is given.

DR. GOLD: These very interesting experiments cited by Dr. Grace have to do with the reaction of the total person, the influence of mood or attitude on the response to a drug. His examples are drawn from observations on the gastro-intestinal tract but the same can be shown to apply to responses of the blood pressure, the heart, or any other functional system in the body.

Dr. Grace points out that we fall short of understanding the effect of a drug unless we observe it in action during different emotional states and he suggests that in the evaluation of a drug we should first ascertain and define the patient's mood or attitude. Perhaps we can have some discussion of another approach to the evaluation of a drug, one that does not necessarily require such definition of the patient's emotional state. I have reference to a comparison of one compound with another, an attempt to determine, for example, by how much one compound is more potent than another in relation to a particular effect. The moods and attitudes of the patients used in such comparisons are very important and influence the results but it is possible so to design the evaluation that whatever influence the emotional state of the patients may exert is canceled out by having it distributed equally between the two compounds used in the comparison. The two compounds may involve an allegedly potent agent and a blank of such physical properties as to render a distinction between the two impossible except through some pharmacologic potency which may exist. On the other hand, the two compounds may both be potent and we test them to determine a difference in potency. In this type of evaluation of a new drug there are two indispensable elements: one is the notion of a comparison of one thing with another, the other is the factor of the double-blind procedure which calls for such an arrangement of the investigation that neither the patient nor the doctor is aware of the identity of the two agents until the results are in and analyzed. This is imperative to avoid the influence of subconscious bias. The failure to use the double-blind test and the placebo in the attempt to evaluate a new drug is responsible for a large proportion of erroneous conclusions in clinical testings. It is particularly noteworthy in drugs used for the treatment of gastrointestinal symptoms, hypertension and angina pectoris. I am not sure why it is that the use of a placebo is considered by many physicians objectionable in a method of clinical evaluation and why there seems to be so much resistance to the idea that the experimenting doctor and the patient should remain in the dark about the identity of the agent until the comparison is finished.

DR. FRANK C. FERGUSON, JR.: Dr. Grace has cited examples showing how the patient's moods can influence the effects of a drug. Could we hear

something about the influence of the doctor's attitude on the effects of a drug?

DR. GOLD: It is not difficult to find examples of the profound influence of the doctor's attitude. The case of khellin is a good illustration of recent vintage. This material was introduced a few years ago for the treatment of cardiac pain in coronary disease and for bronchial asthma on the basis of laboratory experimentation showing that it exerts a potent smooth muscle relaxing action. Clinical trials proved that by far the larger proportion of patients with angina pectoris obtained partial or complete relief with this drug. A placebo was used in some of these studies but the physician knew which was which at the time of his questioning the patients. A group of us undertook the investigation of khellin by the double-blind test, using a placebo which in physical appearance was indistinguishable from the tablets of khellin, and arranged observations in such a way that neither the patient nor the doctor was aware of the identity of the two materials until the results were all in and analyzed. After some 3,000 answers regarding the effect on pain of the placebo and khellin given to the same group of patients, the results showed that if the patient and the doctor were kept in the dark regarding the identity of the agents, the placebo and khellin could not be distinguished with respect to the effect on cardiac pain.

The whole history of therapeutics, especially that having to do with the action of drugs on subjective symptoms, demonstrates that the verdict of one study is frequently reversed by another unless one takes measures to rule out the psychic effect of a medication on the patient and the unconscious bias of the doctor. The double-blind test insures this.

DR. FERGUSON: You speak of the need for the double-blind test in cases where drugs are tested for their effects on subjective symptoms. How about so-called objective matters? Do you believe that the double-blind test is necessary there to avoid error in interpretation?

DR. GOLD: I think it is well that you used the term "so-called" objective. I am beginning to wonder whether there are any truly objective observations. In the study of drugs in hypertension, a measurement of the blood pressure would certainly seem to be an objective criterion but I have a notion that the reading of the blood pressure also depends on how the doctor feels about the agent. Subconscious bias is a very

subtle mechanism. Results of a study gain considerably in validity if the doctor making the observation, subjective or objective in nature, does not know whether it is the placebo or the medication in question he is concerned about.

DR. BENJAMIN JABLONS: How important would a placebo be in evaluating the potency of a diuretic agent?

Dr. Gold: In that case, of course, the particular agent is compared with a standard. What would you think, Dr. Cattell, about the need for a double-blind test in a comparison involving a diuretic effect as a measure?

DR. McKeen Cattell: It should be done as a double-blind test. There is always the possibility of a subjective element coming into the experiment at one point or another and influencing the results.

DR. PAUL REZNIKOFF: One of the least subjective measurements is that of the iron content of the blood in an anemic patient when following the improvement in the hemoglobin value during medication. Attempts are made to diminish dependence on subjective impressions and verify results with hemoglobin values and hematocrit readings. In these patients attempts have been made to determine the relative value of various iron compounds and on the basis of such objective measurements it has been stated that some forms of iron are more effective than others. However, if one views the objectives in these cases in more common sense terms, it is extremely difficult to find any substantial difference in the efficiency of iron compounds. I wish to suggest that when one is dealing with human beings, it is very difficult to have a purely objective measurement.

Dr. Gold: You mean that in all so-called objective studies or studies using objective measurements, subjectivity seems to creep in somehow.

Dr. Reznikoff: Yes, honest subjectivity. I do not refer to those cases in which a person wishes to prove something.

DR. GOLD: I am glad to hear you say "honest subjectivity." I think it is a matter of the greatest importance to recognize that the bias on the part of doctors that is most serious is the unconscious bias, the kind of thing of which the doctor, himself, is not aware.

I think Dr. Reznikoff has pointed up an important factor in the comparison of therapeutic agents, namely, the selection of appropriate criteria for judging total results. A comparison

of iron preparations in the treatment of anemia by the measurement of red cells, hemoglobin and hematocrit may possibly show differences between one compound and another, which fail to emerge when a comparison is made in terms of the well-being of the patient as a whole.

DR. CATTELL: Dr. Grace's results are certainly significant in showing the importance of different mood states in relation to the action of a drug. In this connection, however, there is another point which seems to me of great value to the physician, and that is the fact that he would like to know what the reaction to a particular agent is likely to be in the general population. The doctor has to start somewhere. Studies of a drug should provide him with some notion as to the probability of the drug proving useful in a particular situation. If we use a suitable control agent, we can determine whether the particular drug is better than another or has the same effect as another on the average population.

DR. GOLD: What Dr. Cattell has just said touches on an important aspect of the comparison of drugs in humans, namely, the matter of selection of suitable patients for investigation. If it is something about the general population that one is looking for, then the study patients must be truly representative. The same applies if the problem relates to some specific class of patients.

DR. ROBERT D. HUEBNER: How are you going to do the double-blind test in a situation such as anticoagulant therapy in which the doctor has to prescribe or order a day-to-day dose on the basis of the prothrombin test? He has to know the result of this objective test before he can prescribe.

DR. GOLD: You are quite right if what you are thinking about is a doctor treating a patient. When he does that he has in effect already assumed that dicumarol is valuable and he proceeds to use it. That, however, is not what we are discussing. We are talking about investigating a drug, let us say in this case dicumarol. Now we are in the position of trying to determine whether it is valuable. In such a situation the double-blind test is imperative and the difficulty you mention is easily overcome by having one person carry through the dicumarol treatment while another person to whom the nature of the treatment remains unknown, whether placebo or dicumarol, makes the decisions concerning the clinical course and complications.

Dr. Huebner: But if the patient begins to bleed, the doctor and the laboratory person will have to get together to find out whether or not it is due to the dicumarol.

DR. GOLD: Yes, that is correct. This would interrupt the experiment. One might add that if the person in charge of the dicumarol dosage and prothrombin testing keeps a close watch on the situation, the effects should rarely if ever get out of hand and bleeding due to dicumarol should rarely occur.

DR. WALTER MODELL: Dr. Gold, one of the problems that presents itself during the investigation of a drug arises from the fact that the patient himself may know that he is the subject of an investigation. This information is highly charged and may have a bearing on the results. Perhaps you might wish to elaborate on this point.

DR. GOLD: It is a very important point. The impact of the patient's knowledge that the medication is part of an investigation is properly distributed only when all patients are treated. Do not have a treated and an untreated patient in the study. Treat them all with a tablet, or a solution, or an injection, as the case may be, one with the allegedly potent agent and the other with something that looks, tastes and smells exactly like the first but is a dud. All the patients in the study should appear to be exposed to the same things.

DR. HORACE S. BALDWIN: I believe this point has already been made, but I should like to refer to our own experience in allergy which leaves us with little doubt that a placebo may cause considerable improvement in the patient's symptoms. We had an opportunity to compare a vaccine for hayfever with a placebo. We did not do the double-blind test because the doctor knew which the patient was receiving. The results were unequivocal in showing the value of a placebo in a "subjective" illness.

DR. GOLD: The significance of your point about patients showing improvement in symptoms as the result of a placebo cannot be overemphasized. It can be demonstrated in about 30 or 40 per cent of all patients with all sorts of disorders. This fact is responsible for the vast literature on drugs that have come into therapeutics with high promise and have left the scene with little loss.

DR. SOLOMON GARB: Is a placebo necessary in relation to mortality rates for treated and untreated cases?

DR. WILLIAM T. FOLEY: I would like to make a point here in regard to mortality statistics as related to our study on dicumarol in coronary thrombosis. We placed most dependence on the course of mortality rates. The design of the study called for the alternate case method of treated and untreated cases in the sixteen hospitals. We were a bit troubled, however, by the fact that in some instances this plan for the selection of cases was disturbed. Here was a new drug supposed to be helpful for a disease which carried a high mortality. The word soon got around among the patients in the hospitals and among the families that certain patients were receiving the drug and others were not. In many instances great pressure was brought to bear to see that certain cases would receive it. It raised some question in our minds as to how far one might properly go in judging the value of a method of therapy by the mortality statistics.

DR. GOLD: This is just one more illustration of the importance of seeing to it that there are no untreated cases in a study of a new drug or treatment.

Dr. Reznikoff: We have in the audience an authority on this study, one of our alumni, Dr. Quick. I wonder if we could have some of his impressions.

DR. ARMAND J. QUICK: I agree fully with the stress which has been placed here on the doubleblind test. Specifically, in the matter of anticoagulant treatment of heart disease I think that a valid evaluation requires that one person governs the dicumarol, that another looks after the patient and that a third evaluates the treatment. No matter how honest we try to be, if we become enthusiastic we are carried away, and in some manner or other transmit the enthusiasm to the patient. I have made the remark on other occasions that the more impressive the clinician, the more engaging his personality, the worse he is from the standpoint of evaluating drugs, because his personality very often dominates the patient.

DR. GOLD: I suppose that what you are suggesting is that we should not try to alter the personality of the investigator but let him enjoy whatever personality he has and neutralize the bias it might create by balancing the effects of the drug against the placebo.

DR. QUICK: That is the point.

DR. GOLD: I wonder if we might have some comments on this subject from Dr. Bross who is an expert in vital statistics and has had much to

do with designs for the investigation of therapeutic problems.

DR. IRWIN D. J. BROSS: I am very much impressed with the remarks I heard today. It seems as though this group has a level of sophistication that I have not often encountered in my work with medical groups. I might say a word about this third person who was mentioned by Dr. Quick. I guess this is more in the nature of a statistician's type of third person. He can be replaced by a machine. The reason I mention this is that frequently it is inconvenient to have the decisions made by a third person. There are many situations in which decisions can be made by a pair of dice which represent a third person in this particular sense. If a pair of dice sounds unscientific, you can call it randomization, and you can use a random number table which is perhaps not as illegal looking as a pair of dice.

DR. FERGUSON: Since the matter of statistics has been brought up, I should like to remark that I have an intense prejudice against the mass of statistics that accompanies the introduction of new drugs. It seems to me that statistics as they are so often used are too often misleading. Many people believe that they eliminate chance when in fact they merely give an idea as to the probability of the results being due to chance. There is also the fact, which is often overlooked, that statistical analysis of the results does not correct the defect of a bad experiment.

Dr. Bross: Yes, but I want to point out where statistics do come in. Actually, there are two things which interfere with the evaluation of drugs. The first is what might be termed the experimental error, sampling variation. This is essentially the factor that is supposed to be controlled by statistics. The second thing is the particular factor that has received special attention at this conference, namely, bias. The standard statistical tests do not in themselves control bias. Analysis by statistical technics is based on the assumption that the results are unbiased. I would agree, therefore, that there is a great deal of statistical, or presumably statistical, material that is published which is completely misleading simply because of the belief that all

that is necessary to solve a problem is to put down a little statistical arithmetic. Much more than that is necessary. The problem is much more complicated.

DR. GOLD: I presume that the item to which you refer is the design as to bias before the experiment is actually carried out.

DR. Bross: Yes, the design as to bias.

SUMMARY

DR. GOLD: This conference directed its attention to the problem of the clinical evaluation of new medicinal agents as one of the major issues in therapeutic progress: How to secure verdicts in the comparison of one drug with another which stand a reasonable chance of escaping reversal. In an account of interesting experiments on the gastrointestinal tract it was pointed out that the effect of a drug varies greatly with the patient's mood and that the effect may be significantly altered with a change in the mood. The discussion indicated how such factors might change results in the evaluation of a therapeutic agent. Special attention was directed to the use of the placebo, the double-blind test, statistical analysis of the data and experimental design to eliminate bias. Emphasis was placed upon the unconscious aspects of bias of the physician, a subtle mechanism which contrary to his best intentions may give rise to misleading results. It was a noteworthy feature of the various discussions that the control of this factor by the doubleblind test is now recognized as imperative for the valid evaluation of medicinal agents, not only with respect to the study of subjective symptoms such as cardiac pain but also in studies involving so-called objective measurements such as iron in anemia, diuretic agents and anticoagulants in thrombotic diseases. The conventional design of the treated and untreated groups in a clinical evaluation of a medicinal agent is giving way to the plan which calls for treating all patients, where possible, with the agent in question or with a placebo, the two being indistinguishable in physical form or appearance and their identity unknown to patient or investigator during the experiment.

Clinico-pathologic Conference

Substernal Goiter, Thyrotoxicosis, Tracheal Compression and Pulmonary Disease

S TENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. M. (No. 224798), was a sixty-six year old white housewife, who entered the Barnes Hospital for the first time on July 4, 1953, complaining of shortness of breath and difficulty in swallowing of approximately eighteen months' duration. The family history disclosed that one brother had died from carcinoma of the rectum and one sister from carcinoma of the uterus. The patient had been in good general health until shortly after the birth of her second child, when, at the age of thirty-seven, she became aware of an enlargement of her neck. Shortly thereafter she began to experience episodes of shortness of breath on exertion, asthmatic wheezing, and on occasion required three pillows in order to sleep. At about this time bowing of her upper spine began to develop, which progressed very slowly, producing a noticeably stooped appearance.

The respiratory symptoms remained as described until eighteen months before entry, at which time she had marked increase in dyspnea and orthopnea. She noticed that all her fingers swelled and that the veins over her anterior chest became prominent. Over the next twelve months she manifested definite heat intolerance, periods of great anxiety, gradual loss of appetite and a weight loss of sixty pounds. She became chronically hoarse and had a constant cough productive of small amounts of blood-streaked sputum. Difficulty in swallowing was noted at about this time and progressed rapidly until all her food intake was in liquid form. Two months prior to admission she suffered severe left anterior chest pain and was hospitalized elsewhere for eighteen days; however, she was ambulatory during most of this period. The results of the examination during this hospitalization were not known, but she was discharged from the hospital on a regimen consisting of a low salt diet and one tablet of digitalis leaf daily. Shortly thereafter her dysphagia increased; three weeks prior to admission she was frightened by lightning, screamed and thereafter was unable to speak audibly. She became bedridden, and demonstrated rapid increase in all her symptoms until she was brought to the Barnes Hospital.

Physical examination at the time of admission revealed the patient's temperature to be 37.8°c., pulse 120, grossly irregular but without deficit, respirations 36 and blood pressure 125/80 in both arms. She was extremely debilitated and unable to speak above a whisper. She was orthopneic and coughed frequently, bringing up small amounts of blood-flecked sputum. The skin hung loosely, lacking turgor, but was otherwise not remarkable. There was marked kyphoscoliosis of the dorsal spine. The left pupil was larger than the right; there was slight bilateral lid lag and convergence was poor. The fundi were not remarkable. There was no lymph node enlargement, but the thyroid isthmus was twice the normal size, and beneath the left sternomastoid muscle was a firm, rubbery, ill defined mass. The neck veins were markedly distended but did not pulsate. The anteroposterior diameter of the chest was increased. There was dullness to percussion and breath sounds were decreased over the left lower lobe posteriorly. Mediastinal dullness was increased bilaterally in the second interspace. The cardiac impulse was diffuse, extending 10 cm. from the mid-sternal line in the fifth intercostal space. A grade III apical systolic murmur was heard but was not transmitted. No masses were felt in the abdomen but there was moderate tenderness in the right upper quadrant. A massive rectocele was present. There was two plus ankle edema but no clubbing. Neurologic examination was within normal limits except for a marked fine tremor of both hands and hyperactive reflexes.

The laboratory data were as follows: red blood cells, 4,900,000; hemoglobin, 13.1 gm. per cent; white blood cells, 26,750; differential: segmented neutrophils, 78 per cent; stab forms, 9 per cent; eosinophils, 1 per cent; lymphocytes, 11 per cent. There was toxic granulation of the neutrophils; the red blood cells were slightly hypochromic. Bone marrow; within normal limits. Urinalysis: specific gravity, 1.025; pH, 4.5; albumin, trace; sugar, negative; centrifuged sediment, rare white blood cell. Stool: guaiac negative. Blood chemistry: non-protein nitrogen, 21 mg. per cent; sugar, 112 mg. per cent; sodium, 141 mEq./L.; chloride, 88 mEq./L.; carbon dioxide combining power, 29 mEq./L.; alkaline phosphatase, 4.2 Bodansky units. Venous pressure, 146 nm. saline, each arm. Roentgenogram of the chest; marked dorsal kyphosis with hypertrophic osteoarthritis and marked demineralization of bones; cardiac enlargement; elevated left leaf of diaphragm; trachea deviated to the left, apparently due to pressure from a 6 by 8 cm. soft tissue density containing patchy calcification, lying just to the right of the trachea, consistent with aneurysm of innominate artery, or with thyroid adenoma; in the mid-lung field on the left was a soft tissue density interpreted as an interlobar effusion. Electrocardiogram: rapid auricular fibrillation with frequent ventricular premature contractions; digitalis effect.

On admission the patient was given digitalis in the same dose as she had been taking at home, fed a liquid diet which was salt-poor and placed on bedrest. Uptake of a tracer dose of I-131 was 62 per cent. The chest was scanned with a scintillation counter and no localized area of uptake was found. The protein-bound iodine of the serum was $8.5 \mu g$. per cent. On the fifth hospital day bronchoscopy was performed; the left vocal cord was found to be paralyzed and the upper trachea narrowed by external compression. The left main stem bronchus had a markedly granular mucosa; biopsy of this area was interpreted as showing hyperchromatic cells. Cultures and guinea pig inoculation for acid-fast bacilli were negative.

On the sixth hospital day the patient began to receive tapazole[®] in daily doses of 20 mg.; there was little change in her condition for the next two weeks, and on the fourteenth day she was

given a therapeutic dose of I-131. Her white blood cell count continued to range between 25,000 and 30,000, her sputum contained many coliform organisms and she was treated intensively with parenteral penicillin and streptomycin. Chest roentgenograms on the seventeenth hospital day showed an infiltrative process in the right lower lobe; a left thoracentesis on that same day yielded 30 ml. of serosanguineous fluid which had the following characteristics: specific gravity, 1.018; protein, 2.8 gm. per cent; microscopic examination: total cell count, 265,000; cell count with acid, 191,000; differential: segmented forms, 70 per cent. Culture and cytologic studies of this fluid were negative. On her thirty-fourth hospital day the patient was given 35 mc. of I-131. The following morning she was markedly dyspneic; her pulse had risen to 190, the entire left hemithorax was dull to percussion, and breath sounds were absent in that area. A chest roentgenogram disclosed opacification of the entire left chest and a large effusion at the right base. Thoracentesis on the right yielded 400 ml. of turbid fluid with a protein concentration of 4.2 gm. per cent; culture of this fluid revealed Friedländer's bacillus.

Despite intravenous digitalization and continuous oxygen therapy acute pulmonary edema suddenly developed and she died on August 7, 1953.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient presented an unusually interesting diagnostic problem. After the birth of her second child, at the age of thirty-seven, a mass in her neck developed which gave her pressure symptoms, particularly some difficulty in breathing, intermittently for some thirty years. Six months before she was admitted these pressure symptoms increased and physical signs developed in the lungs and heart. Since most of the physical signs were within the thorax, we ought first to look at the x-rays. Dr. Seaman, will you open the discussion?

DR. WILLIAM B. SEAMAN: The initial examination of the chest was made on July 5, 1953. (Fig. 1.) It demonstrated several abnormalities, perhaps the most striking being the presence of a large mass in the superior mediastinum. The trachea was displaced to the left by this mass, which contained flecks of calcium. The mass was interpreted as probably a calcified substernal goiter or an aneurysm_of the innominate artery.



Fig. 1. Postero-anterior chest x-ray taken on admission. The displaced trachea is outlined in black ink.

Roentgenographically, they cannot be distinguished. The cardiac shadow was somewhat enlarged, although the left border was obscured by an elevated diaphragm which did not move on fluoroscopic examination. In addition, there was a mass in the left mid-lung field which was seen in the lateral film to overlie the cardiac shadow and to have a biconvex appearance. Usually biconvex shadows in this region are characteristic of loculated or interlobar effusions. and this was interpreted as such. On the same day films of the lumbar spine, pelvis and skull showed no bony abnormalities. The next chest film, two weeks later, showed a small, ill defined area of density in the right upper lobe, which was thought to be inflammatory in nature. One week later the heart appeared somewhat larger, and there was a little fluid in the left costophrenic angle. In addition to the infiltration in the right upper lobe there was a new, small, rounded area in the right lower lobe, which was interpreted as possibly representing metastatic involvement of the lung. The left humerus showed an irregular area of radiolucency which might have been due to metastasis. The last film, taken on the day of death, disclosed a moderate pleural effusion on the right, a smaller one on the left and an opaque left upper lobe on postero-anterior projection. However, on the

lateral film the lower lobe appeared well aerated, even emphysematous, so that the opacification of the upper lobe might have been due to atelectasis.

In retrospect, one might interpret the changes in the left lung field as deriving from primary disease of the lingula, possibly a tumor, leading to a combination of atelectasis and infected secretions, extending into the remainder of the upper lobe, and finally producing atelectasis of the entire left upper lobe.

Dr. Alexander: We should properly consider next what happened to this woman at age thirty-seven. Dr. Daughaday, would you tell us what sequence of events occurred in her thyroid

gland at that time?

DR. WILLIAM H. DAUGHADAY: This patient probably developed a non-toxic diffuse goiter during her pregnancy; this is a very common occurrence, the cause of which is not known. She may have been suffering from iodine lack before she became pregnant and noticed the goiter only after the birth of her child. The surprising aspect of this history is the development of exertional dyspnea, asthmatic wheezing and severe orthopnea at this time. It is very unlikely that all these symptoms were due to obstruction from a goiter; they are not symptoms of early tracheal compression. In my experience, such symptoms are invariably associated with a very large, easily visible goiter; a small goiter located in the neck of a young person does not produce tracheal compression, although the patient may have a sensation of weight in the neck when lying down at night. Since the symptoms presented by this patient do not impress me as being due to goitrous compression of the trachea, she probably had some independent pulmonary disease to explain her wheezing dyspnea. Subsequently, as the tissues of the neck were stretching themselves to accommodate it, there was a "slipping" of the goiter down the natural fascial planes of the neck, so that part of the enlarged gland came to lie in the superior mediastinum. In the early part of 1952 a rather abrupt change occurred which seems related to her final illness. The symptoms suggest that thyrotoxicosis developed, and the laboratory data are compatible with this diagnosis.

In view of the mild thyrotoxicosis, the large gland and the pressure symptoms—paralysis of one vocal cord, partial Horner's syndrome, and perhaps invasion of the lung—one is tempted

AMERICAN JOURNAL OF MEDICINE

to explain the entire illness on the basis of thyroid carcinoma, but there are other diseases which should be considered.

DR. EDWARD H. REINHARD: One can get pressure symptoms and nerve involvement from a benign nodular goiter, particularly when it encroaches upon the thoracic inlet. The fact that this patient had thyrotoxicosis at the same time she may have had cancer of the thyroid puts her in a rather unusual group. Most patients who have cancer of the thyroid have a relatively low uptake of radioiodine. There is a distinct possibility that this patient had a benign goiter with hyperthyroidism, and that the pulmonary signs may have been related to an independent pulmonary disease.

DR. W. BARRY WOOD, JR.: Would a nodular goiter that is benign react to the radioiodine therapy in the manner displayed in this case, leading to sudden obstruction to the left upper lobe of the lung?

DR. DAUGHADAY: With respect to the reaction to therapy, there is no fundamental difference between thyroid malignancy that takes up radioiodine and hyperfunctioning goiter. We have had some difficulty occasionally with both, but we have had surprisingly little trouble with pressure symptoms, even in feeble elderly ladies whose large goiters were wedged in their thoracic inlets. In only one patient have we seen acute thyroid edema, necrosis and pressure symptoms necessitating tracheotomy.

DR. ALEXANDER: What kind of a goiter did this patient have at age thirty-seven?

DR. DAUGHADAY: Goiters of this type often begin as simple hyperplastic glands, but after the period of growth subsides they become distended with colloid. Certain areas undergo hyperplasia while other areas become atrophic, which is the best-accepted explanation for the origin of adult nodular goiters. Once a nodular goiter has developed, it is subject to two complications, namely, malignant change and toxic hyperplasia. This woman certainly had an underlying nodular goiter. The question is whether her gland underwent both complications.

DR. ALEXANDER: Does the bowing of the thorax, which apparently began at the same time as her goiter, throw any light on the course of her thyroid disease?

Dr. Daughaday: Osteoporosis as a manifestation of hyperthyroidism is not a disease of young persons. It is usually seen in patients with long-standing thyrotoxicosis, most often in

women past the menopause. I cannot explain why kyphosis developed in this patient at such an early age.

DR. EDWARD MASSIE: Could she not have had asthma at that time, which accounted for the development of the emphysema and kyphosis? The goiter would then have been incidental and not pressed on the trachea so many years before her final troubles began.

DR. I. JEROME FLANCE: How accurate is the radioactive iodine uptake in the diagnosis of hyperthyroidism?

Dr. Daughaday: In this part of the world a high uptake of radioiodine is almost always diagnostic of thyrotoxicosis. When the percentage uptake of the tracer dose exceeds 65 per cent, the disease is probably present. The converse is not true. We see a number of patients with nodular goiters and mild hyperthyroidism who have normal uptakes of the tracer dose. In areas such as Argentina, where the soil is very low in iodine, high uptakes are the rule. There are cases of familial cretinism and of large goiters in which high uptakes are found; it seems likely that at some stage in the development of a non-toxic diffuse goiter iodine deficiency occurs; and if one were to give such a patient a tracer dose just at that time, a moderately elevated uptake might result.

DR. DAVID T. GRAHAM: Even if this patient had osteoporosis, it is hard to understand how kyphosis could have developed without x-ray evidence of collapsed vertebrae.

DR. ALEXANDER: Kyphosis may occur without collapse of the vertebrae; the first change is a thinning of the intervertebral discs; emphysema alone produces an increase in the anteroposterior diameter of the chest, but not kyphosis.

DR. DAUGHADAY: One of the puzzling features of this case is that the clinicians felt the mass in the neck on the left, whereas the x-rays showed it to be on the right. Perhaps she had bilateral enlargement, but the right lobe continued to grow and to descend more than the left.

DR. SEAMAN: Isn't it a little inconsistent that the large mass was on the right, but it was her left recurrent nerve and her left phrenic nerve that were compressed? Usually these nerves tend to be invaded or compressed by the very large masses. The discrepancy here makes me raise the diagnosis of primary carcinoma of the lung.

DR. ALFRED GOLDMAN: The same diagnosis suggested itself to me, particularly in the

presence of mediastinal masses and atelectasis of the left upper lobe. The bronchoscopic biopsy mentioned hyperchromatic cells, which may be significant. The pleural fluid was compatible with pulmonary malignancy, even though cytologic study on one occasion was negative.

DR. ALEXANDER: It may be of interest to know how frequently carcinoma of the thyroid invades the lung. I have looked up a number of published series of cases, and find that the lungs were involved in about half of them. I do not know whether carcinoma of the lung ever invades the thyroid.

DR. SEAMAN: In addition to the nerve involvement, a finding which again suggested primary bronchogenic carcinoma was the mass in the left mid-lung field, which was originally interpreted as interlobar effusion. We have seen several cases in which carcinoma of the lingula associated with atelectasis and secretions gave a similar appearance.

DR. ALEXANDER: Dr. Massie, what is your opinion about her cardiac disease?

DR. Massie: The heart disease here was secondary, probably arteriosclerotic in type. The apical systolic murmur may have been due to a dilated mitral ring. To further embarrass her circulation, she had hyperthyroidism as well as severe pulmonary disease. In patients who have rapid auricular fibrillation and slowed pulmonary circulation, it is usual to find multiple pulmonary emboli at autopsy and these may often be the immediate cause of death.

DR. ALEXANDER: Can the auricular fibrillation associated with thyrotoxicosis be treated without treating the thyroid disease?

DR. Massie: Not definitively, of course, but it is remarkable sometimes how well these patients respond to rapid intravenous digitalization plus the use of quinidine. It is usually possible to slow the fibrillation, in any case.

DR. Wood: It is perhaps worth while making a comment on the culture of Friedländer's organism from the pleural fluid. This is not a common laboratory finding, and we must consider that the patient may have had terminal Friedländer's bacillus pneumonia with invasion of the right pleural cavity.

DR. ALEXANDER: The discussion of this case has clearly indicated that the two principal diagnostic possibilities are carcinoma of the thyroid in a toxic nodular goiter and primary carcinoma of the lung with associated hyper-

thyroidism. The consensus of the staff seems evenly divided; my own diagnosis is primary carcinoma of the thyroid.

PATHOLOGIC DISCUSSION

DR. JOHN C. FLETCHER: The thyroid gland was replaced by a large nodular goiter that weighed 300 gm. This goiter (Fig. 2) almost completely encircled the trachea and esophagus and in its mid-portion on the right side it contained a paler, round, encapsulated nodule which measured 6 cm. at its greatest diameter. The thyroid was continuous with a large multinodular substernal goiter which encroached upon the aorta, superior vena cava and the right pleura without invading those structures, although the trachea was compressed in its sagittal plane with several acute angulations. On dissection of the thyroid, several small firm lymph nodes, firmly bound to the thyroid, were present to the left of the midline opposite the lower portion of the right lobe. On cut section they contained foci of very firm, grayish white

Each pleural cavity contained 500 ml. of serosanguineous fluid. The fluid in the right cavity was thicker and more cloudy than that in the left. Very dense fibrous adhesions were present at the base of the left lung and there were fibrinopurulent lesions over the lower lobe of the right lung. A 6 cm. necrotic gray mass was present in the left interlobar fissure; on cut section this arose from a secondary branch of a bronchus to the lower lobe of the left lung. As is shown in Figure 3 the tissue was soft and granular. It engulfed the bronchus and extended into the upper as well as the lower lobe of the lung. Many other small nodules of similar gray tissue were present in the tracheobronchial and cervical peritracheal lymph nodes, the pericardium, kidneys and in several sites in the myocardium. There was bronchopneumonia in the upper and lower lobes of the right lung; a ruptured thin-walled abscess cavity 3 cm. in diameter was present within the area of pneumonia in the periphery of the right lower lobe. Other findings included a small organized thrombus in the right auricular appendage and multiple partially occlusive mural thrombi in the pulmonary arteries. There was also a wedge-shaped infarct 3 cm. in length in the upper lobe of the right lung.

DR. DAVID E. SMITH: Dr. Fletcher has described masses in the thyroid and the left lung

AMERICAN JOURNAL OF MEDICINE

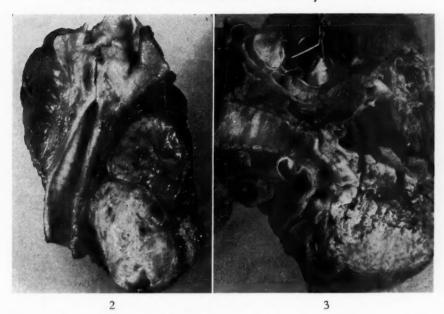


Fig. 2. The posterior aspect of the thyroid and trachea showing compression of the trachea by the mass of the goiter. The lower nodule was scarred and gray. The scalloped upper nodule was mahogany-colored and represented an embryonal adenoma of the thyroid.

Fig. 3. The hilum of the left lung showing granular necrotic carcinoma destroying a secondary branch of the bronchus to the lower lobe.

which obviously contained neoplastic tissue. The contrast between these two tissues is not so vividly seen in the photograph as it was when the tissues were fresh, but the large scalloped lesion in the thyroid was very strikingly different from the gray granular lesion in the lower lobe of the left lung. Figure 4 shows a microscopic section of the scalloped mahogany-colored central lobule in the right lobe of the thyroid. It had a trabeculated pattern typical of an embryonal follicular adenoma of the thyroid. The mass was well encapsulated and showed no evidence of invasion of its capsule or the surrounding compressed and atrophied thyroid. The small nodules which were described grossly in the lymph nodes to the left of the trachea at this level were all related to the tissue in the lungs rather than that in the thyroid.

The problem of hyperthyroidism in this case is interesting and can hardly be ascribed to the adenoma. Adenomas of this type are very rarely hyperfunctional by any criteria. Increased absorption of radioactive iodine is said to occur in only about 10 per cent of cases of embryonal adenomas, or in less than 1 per cent of the total number of adenomas of the thyroid. A radioautograph was made of a section taken through the edge of the adenoma and the degenerated goitrous nodule below it. The photographic plate was burned very severely in the regions

under the tissue of the colloid goiter and not at all in the region of the adenoma. This is good evidence that the adenoma was not responsible for the abnormally high uptake of iodine. As is often the case, search of the remainder of the thyroid tissue for morphologic evidence of hyperplasia to correlate with the clinical evidence of hyperthyroidism was somewhat disappointing. There were areas of thickened epithelium of the dilated acini in some of the better preserved portions of the thyroid. (Fig. 5.) The large mass below the adenoma, as well as many other portions of the goiter, was largely fibrous tissue, containing areas of degeneration typical of a nodular goiter. Areas of slight hyperplasia within various regions of a nodular goiter are not specific anatomic evidence of clinical hyperthyroidism by any means. They are more a reflection of the pathogenesis of these lesions, as Dr. Daughaday explained; namely, an asynchronous growth of different parts of the thyroid under varying stimulation. The total mass of this thyroid may have had more to do with the amount of radioiodine taken up than did any distinctly hyperplastic character of the epithelium.

Sections of the mass in the bronchus of the lower lobe of the left lung, such as Figure 6, showed the irregular architecture typical of any epidermoid carcinoma. Similar tissue was also present in the various lymph nodes, kidneys and

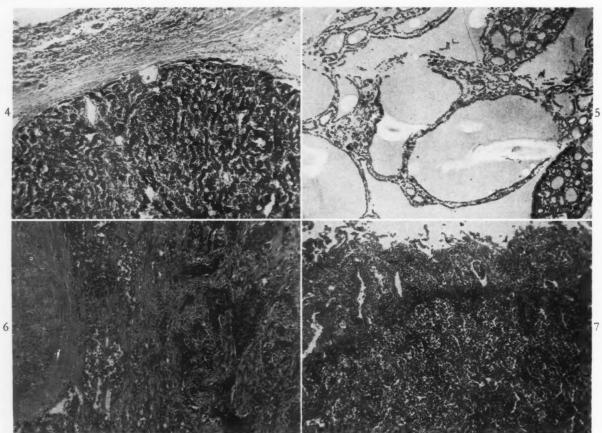


Fig. 4. A section of the mahogany nodule in the lower portion of the right side of the thyroid showing the trabeculated pattern of an embryonal adenoma with no signs of invasion of the capsule.

Fig. 5. A section of the better preserved portion of the thyroid showing slight thickening of the epithelium lining a few acini. These were the most suggestive changes of epithelial hyperplasia seen in sections of an otherwise typical adenomatosis goiter with many foci of degeneration.

Fig. 6. A section of the bronchus to the lower lobe of the left lung showing masses of epidermoid carcinoma.

Fig. 7. A section of the wall of the abscess in the lower lobe of the right lung showing that it was principally an area of necrosis within bronchopneumonia with relatively little organization or fibrous response.

myocardium. The heart itself was minimally enlarged. It weighed 300 gm. with attached aorta, which is within the upper limits of normal for a woman, even though this patient was emaciated. The coronary arteries contained only a few arteriosclerotic plaques. There was, therefore, no evidence of any degenerative vascular disease or hypertension that might have been responsible for the cardiovascular symptoms and signs. The multiple metastases to the myocardium and the pulmonary disease offered a better correlation with the evidence of heart disease suggested in the clinical discussion.

The last illustration (Fig. 7) is a slide from the wall of the abscess in the periphery of the lower lobe of the right lung. This lesion was situated posteriorly behind the diaphragm in a position that would have been difficult to demonstrate radiographically. It was a cavity lined by a

necrotic membrane, not the usual dense granulation tissue of a well established lung abscess, but rather necrosis within an area of pneumonia. This cavity was in communication with the pleura and was undoubtedly the source of the right empyema.

In summary, this was the case of a woman with a large nodular goiter that had sunken into a substernal position, or may have partially arisen there, and in which at some time an independent embryonal follicular adenoma developed. These lesions seem to be unrelated to the most dramatic symptoms of her last admission, although compression of the trachea had undoubtedly been present for a considerable period. The bronchogenic carcinoma involving the left hilum and invading the surrounding structures was responsible for the symptoms of dysphonia, dysphagia and accen-

tuated dyspnea that occurred within the last eight months. Terminally, bronchopneumonia and evidences of cardiac arrythmia developed, the causes of which may have been contributed to by the pneumonia, the thrombi in the pulmonary arteries or the carcinomatous metastases to the myocardium. Late in her course there was a rupture of an abscess within the bronchopneumonia in the lower lobe of the right lung and the establishment of an acute empyema. The shadow in the right lung seen on the second roentgenogram probably represented the infarct in the lower lobe of the upper lung.

DR. DAUGHADAY: The anatomic interpretation of thyroid tissue with respect to the amount of thyroid hormone it is producing is very difficult and often correlates poorly with hormonal studies, particularly in patients with moderate hyperthyroidism. We know hyperthyroidism can recur when there are only about 5 or 10 gm. of thyroid tissue. In a large goiter such as this patient's it is quite possible there were 50 or 100 gm. of functioning tissue producing 25 to 50 per cent more hormone than

normal without showing the cellular hyperplasia usually associated with advanced degrees of hyperthyroidism. The protein-bound iodine value was also within the upper limits of normal because moderate hyperthyroidism can apparently be produced by only a moderate increase of thyroid hormonal production.

Final Anatomic Diagnoses: Bronchogenic epidermoid carcinoma of the lower lobe of the left lung with metastases in the peritracheal lymph nodes, myocardium, pleura, kidneys and pericardium; adenomatous goiter with substernal extension; embryonal follicular adenoma in the right lobe of the thyroid with compression of the trachea and esophagus; bronchopneumonia in the right lung with acute abscess in the lower lobe and rupture into the right pleural cavity; multiple mural and partially occlusive thrombi in small branches of the pulmonary arteries; partially organized infarct in the upper lobe of the right lung.

Acknowledgment: Illustrations were made by the Department of Illustrations, Washington University School of Medicine.

Necrotizing Angiitis Asssociated with Chronic Ulcerative Colitis*

FRED WASSERMAN, M.D., ARTHUR KROSNICK, M.D. and HENRY TUMEN, M.D.

Philadelphia, Pennsylvania

HRONIC non-specific ulcerative colitis is a disease of uncertain etiology and pathogenesis. The causes of the so-called necrotizing angiitides also are unknown. The coexistence of these two entities in the same patient is very unusual and is of interest because it may shed some light on our understanding of the two disease states. We wish to report on a patient in whom the clinical, laboratory, pathologic and radiologic findings confirm the presence of allergic granulomatous angiitis that developed during the course of non-specific ulcerative colitis of the chronic, continuous type and to discuss the possible relation between these disorders.

CASE REPORT

H. B., a twenty-one year old white male, was first admitted to the Graduate Hospital on September 30, 1952 because of a generalized convulsion which had occurred approximately twenty-four hours previously. The following details of a protracted illness were subsequently uncovered.

The family history disclosed only that the father had asthma. In regard to previous illness, the patient had the usual childhood diseases without sequelae. At the age of nine he had scarlet fever. There was no history of operation or injury.

In April, 1943, at the age of ten, this patient was first studied at another institution because of diarrhea and intermittent colicky abdominal pain of about six months' duration. For two days prior to that admission he had had profuse diarrhea and had passed several stools which contained gross blood. Examination of the stool disclosed cysts of Entamoeba histolytica. He was treated with emetine, carbarsone, chiniofon

and sulfasuxidine. Although he received several courses of sulfonamides and his stools became free of E. histolytica cysts, the diarrhea persisted. He was studied with repeated endoscopic examinations and barium enemas over an interval of three months. Gradually he developed the clinical picture of chronic ulcerative colitis, and he was finally discharged with this diagnosis. He has continued having between five and eight diarrheal stools per day from 1943 to the present writing. Excessive mucus and flecks of red blood are frequently noted and cramping pain has been common. Multiple blood transfusions have been necessary during repeated hospitalizations.

Except for colonic symptoms and an insidious but progressive weight loss, the patient apparently did fairly well after his discharge in 1943 for he remained out of a hospital from 1943 to 1949. In December, 1949, at the age of sixteen he was again studied at another hospital because of a chronic cough and wheezing. He was said to have improved on aureomycin therapy. Because he complained of muscle pain and paresthesias of the left arm and hand of approximately four days duration, a gastrocnemius muscle biopsy was performed. The microscopic section showed "numerous inflammatory cells scattered through the muscle and fascial planes and surrounding veins and thick-walled arterioles. The arterioles showed marked proliferation of the intima. In the adventitia, inflammatory cells are numerous." The diagnosis was "subacute allergic arteriolitis." (Fig. 1.)

One month later hospitalization again became necessary because of paresthesias of the feet. At this time skin testing, as part of an allergic evaluation, disclosed marked sensitivity

^{*}From the Departments of Gastroenterology and Medicine, Graduate Hospital of the University of Pennsylvania, Philadelphia, Pa.

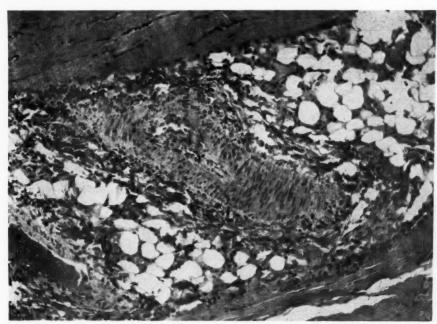


Fig. 1. December, 1949. Biopsy of gastrocnemius muscle. Note the numerous inflammatory cells scattered through the muscle and fascial planes and surrounding the vessels. The walls of the artery are thickened and contain inflammatory cells. (Photomicrography courtesy of Dr. Henry Brody.)

to numerous inhalants and foods and desensitization was begun. Chest x-ray revealed paratracheal and hilar lymph node enlargement. Biopsy of an enlarged axillary node showed "hyperplastic germinal centers, lymphocytic infiltration and thickened arteriolar walls." A barium enema now disclosed involvement of the entire colon by ulcerative colitis and interval examinations up to the time of writing have verified the changes of far advanced ulcerative colitis from the rectum to and including the cecum. (Fig. 2A and B.) Repeated upper gastrointestinal roentgenograms have never disclosed any involvement of the distal ileum and all small bowel examinations have been essentially negative.

In May, 1950, the patient was again readmitted to another hospital because of an exacerbation of asthma. Adrenalin, benadryl, aminophyllin, oxygen, terramycin and aureomycin are said to have terminated the attack after three weeks and he was discharged.

The following month he was rehospitalized for asthma, a flare-up of his colitis and a skin eruption. Finally in September, 1950, after a three-month hospital stay he was discharged.

The final admission to other institutions came in December, 1950, precipitated by transient loss of vision and headaches. While in the hospital deep ulcerations over the dorsum of both feet and both ankles developed. It was during this hospitalization that he was first started on cortisone, and he has continued to take this intermittently, alternating with ACTH, up to the present time.

In November, 1951, he had a solitary episode of tinnitus, objective vertigo, nausea and vomiting which disappeared spontaneously after three days.

The patient was first admitted to the Graduate Hospital in September, 1952, because of a generalized convulsion. By this time he was twenty years of age. Except for scattered expiratory wheezes throughout both lungs and discrete, circumscribed chronic ulcerations over the dorsum of the feet and ankles, a complete physical examination was unremarkable. Blood pressure was 120/70. A detailed neurologic examination failed to disclose any abnormality. The significant laboratory findings included albuminuria with an occasional leukocyte and red blood cell in two urine examinations; 35 per cent phenolsulfonphthalein excretion in the first fifteen minutes; sedimentation rate of 29 mm. (corrected) in one hour; a biologic false positive serologic reaction; 30 per cent bromsulphalein retention; 3 (plus) cephalin flocculation; 2 (plus) thymol flocculation and normal thymol turbidity. There was a hyperglobulinemia of 5.0 and 5.3 with a total protein of 9.0 and 8.3 gm./100 cc.

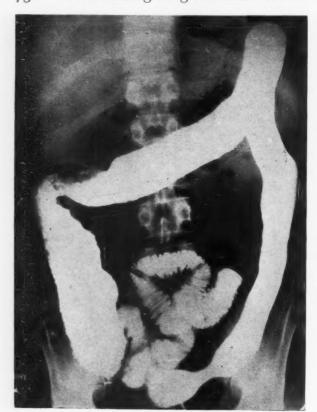


Fig. 2A. Barium enema showing involvement of the entire colon by far advanced ulcerative colitis.

respectively. Chamber eosinophil counts (Table I) were markedly increased prior to ACTH therapy, and a bone marrow examination revealed a marked eosinophilia; there were no

TABLE I

Date	Before ACTH	After ACTH
September 1953		
Chamber eosinophil counts	5,000	68
	4,501	31
November 1953	,	
Chamber eosinophil counts	10,016	50
Leukocytes	18,600	16,600
Neutrophils %	19	78
Lymphocytes %	26	21
Monocytes %	1	1
Eosinophils %	53	
Basophils %	1	

L.E. cells present, an occasional "tart-cell" was seen.

An electroencephalography was interpreted as "definitely abnormal record with a wide-spread disturbance in cerebral physiology." Electrocardiogram and lumbar puncture were normal.



Fig. 2B. Cecum and ascending colon enlarged to show details of advanced ulcerative colitis.

Because of the impaired liver function a needle biopsy of the liver was performed. The microscopic sections of this showed "lymphocytic infiltration of the portal area and small foci of cellular infiltration within the lobule. The Kupffer cells were slightly increased in number." For lack of a more precise term this was classified as "hepatitis." A gastrocnemius muscle biopsy revealed only a very "slight increase in interstitial cells represented by fibroblasts and the cells of the muscle fibers themselves. The arterial elements showed no sign of pathology." The patient responded well to anticonvulsive therapy and ACTH and was discharged.

We next saw the patient in December, 1952, because of a second grand mal seizure. Eosinophilia was again prominent. A lumbar puncture showed only increased pressure and this was verified by a second spinal puncture. Ophthalmologic and neurologic examinations were unrevealing. Skull x-rays and a combined pneumo-ventriculogram were negative. A biopsy of one of the leg ulcers prior to the patient's

AMERICAN JOURNAL OF MEDICINE

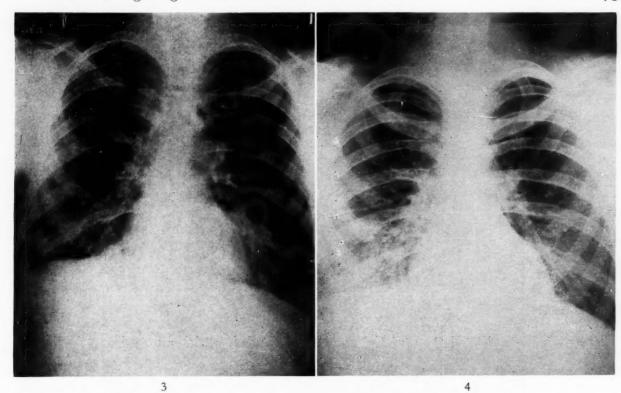


Fig. 3. November, 1953. There is an increase in the pulmonary vascular markings throughout both lung fields. The hilar areas are prominent bilaterally.

Fig. 4. January, 1954. Note extent of infiltration and progression as compared with Figure 3.

discharge disclosed changes of "a non-specific indolent ulcer."

During the next six months (January through June, 1952) recurrent generalized convulsions necessitated several hospital admissions, and increasingly large doses of combined anticonvulsive drugs were necessary to keep him free of seizures. He consistently complained of abdominal pain relieved by defecations, which averaged about six per day. The stools were watery and at times contained gross blood along with large amounts of mucus. He was sigmoidoscoped many times during this interval and the picture of classic, advanced chronic non-specific ulcerative colitis was substantiated. One examiner described the sigmoidoscopic findings as follows:

"The mucosa of the entire rectum is pitted and granular in appearance. Diffuse bleeding results from swabbing with cotton applicators and reveals multiple pin-point ulcerations. No polypoid hyperplastic changes are seen. The bowel wall is somewhat stiffened and the lumen is narrowed. These are the findings indicative of chronic idiopathic ulcerative colitis in a state of subacute activity. The scope was introduced only five inches to avoid unnecessary trauma."

In July, 1953, an exacerbation of the ulcerative colitis resulted in readmission to the hospital, and at this time his spleen was first discovered to be enlarged. Hepatomegaly was also present and persists. The patient was now thin and pale and appeared chronically ill. The hospital course was protracted but he slowly responded to diet, atropine, phenobarbital and intravenously administered ACTH and was again discharged and followed as an outpatient. Frequent asthmatic attacks were treated with ACTH-Gel, and as a rule these improved. Eosinophilia (as high as 38,250/cu. mm.) present before each course of hormonal therapy fell to well within the normal range after ACTH was given, and he was almost symptom-free whenever the chamber eosinophil counts were normal.

In November, 1953, malaise, anorexia and weight loss resulted in still another hospitalization and at this time he was discovered to have a grade III mitral systolic heart murmur. He was afebrile. Significant laboratory studies revealed a red cell count of 3.3 million with 9.7 gm. of hemoglobin; albuminuria, 2 to 3 leukocytes with an occasional red cell and many hyaline casts; phenolsulfonphthalein excretion of 20 per cent in the first fifteen minutes and a blood



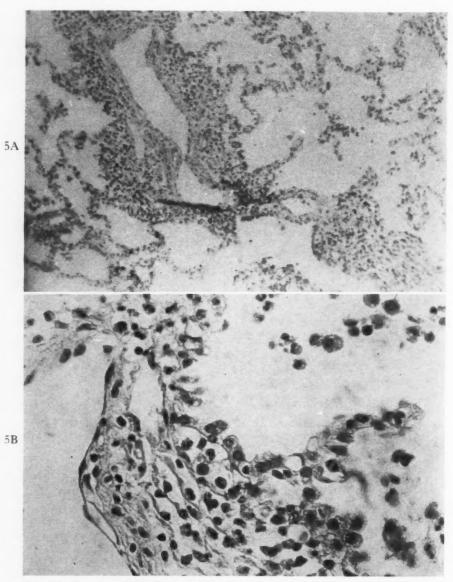


Fig. 5A. January, 1954. Intercostal pulmonary biopsy showing perivascular and interstitial infiltration with eosinophils. The vessel wall is also infiltrated. All of the infiltrating cells are eosinophils.

Fig. 5B. January, 1954. Intercostal pulmonary biopsy enlarged to show details.

urea nitrogen that ranged between 22 and 28 mg./100 cc. Electrophoresis of the serum proteins showed "a decreased albumin fraction and an elevated gamma globulin fraction." Sedimentation rate and twenty-four-hour urinary ketosteroid excretion were within normal limits. An electrocardiogram was reported as being normal. The chest x-ray (Fig. 3) disclosed diffuse prominence of the pulmonary vasculature. Eosinophilia was pronounced. (Table 1.) The patient again improved symptomatically after ACTH and was discharged.

A grand mal convulsive seizure necessitated another admission to the Graduate Hospital in December, 1953. Electroencephalography showed maximal dysfunction without a definite focus. X-rays of the chest now disclosed moderate increase in the pulmonary vascular markings throughout both lung fields. (Fig. 4.) An intercostal pulmonary biopsy was done under local anesthesia. This revealed "a marked eosinophilic infiltration characterized by the presence of many well preserved eosinophilic leukocytes within the alveoli, intermingled with a certain number of enlarged monocytes or macrophages. In addition there were masses of eosinophils in the vicinity of both veins and arteries. Finally, some of the larger arteries showed distinct eosinophilic infiltration of their muscular coats unattended by necrosis or degeneration of the

muscle." (Figs. 5A and B.) This was interpreted as "eosinophilic pneumonia" although perhaps "eosinophilic infiltration of the lung" might be a better term. The patient again responded well to anticonvulsives and intravenously administered ACTH and was discharged.

He is now being followed as an outpatient; occasionally he complains of cramping lower abdominal pain, and frequent diarrheal stools flecked with red blood and containing excessive mucus continue as daily occurrences. A recent biopsy of the rectal mucosa on February 9, 1954, disclosed "active non-specific chronic ulcerative colitis; there is no arteritis and no eosinophilic infiltration."

Summary. This twenty-one year old white male initially presented the clinical picture of chronic idiopathic ulcerative colitis. Some time following this asthma, paresthesias of the hands and feet and generalized convulsions developed, and hepatomegaly, splenomegaly, a diffuse infiltration of the lungs, persistent eosinophilia, a heart murmur and progressive renal impairment have become apparent. A muscle biopsy seven years after the onset of chronic continuous idiopathic ulcerative colitis revealed "subacute allergic arteriolitis," and a lung biopsy now shows eosinophilic infiltration.

COMMENTS

Zeek and others 6.17,18 have attempted to classify inflammatory lesions of blood vessels according to pathologic and clinical criteria rather than to include them all under the name "periarteritis nodosa." Using the generic term "necrotizing angiitis," Zeek subdivides this into five types: (1) Hypersensitivity angiitis, (2) allergic granulomatous angiitis, (3) rheumatic arteritis, (4) periarteritis nodosa and (5) temporal arteritis. Rheumatic arteritis, hypersensitivity angiitis and temporal arteritis need not be discussed here since they bear no relation to the problem presented by our patient.

Both periarteritis nodosa and allergic granulomatous angiitis, however, are of interest in connection with this case. Clinically, periarteritis nodosa is a "multiple system disease" characterized by fever, hypertension, arthralgia, weight loss and a variety of symptoms that result from involvement of the kidneys, gastrointestinal tract, lungs, peripheral and central nervous systems, heart and skin. It is characterized by remissions and exacerbations and is generally of short duration, although a protracted course

may occasionally occur. The gastrointestinal tract is often involved, the lesions being caused by either interference with the blood supply as a result of vascular occlusion (anemic infarcts) or hemorrhagic infarction secondary to vascular wall damage. ¹⁶ One must note that many reports referring to the pathologic findings in periarteritis nodosa do not distinguish this entity from allergic granulomatous angiitis and some of the cases might better fit the latter syndrome.

Wold and Baggenstoss 16 reviewed thirty cases of periarteritis nodosa and described segmental vascular involvement showing medial necrosis and/or cellular infiltration, fibroblastic proliferation, intimal thickening, thrombosis, aneurysms and occlusion, depending on the stage of the disease. Vessels of all sizes were involved throughout the entire gastrointestinal tract, from stomach to rectosigmoid. Among sixty cases of mesenteric arterial occlusion studied by Johnson and Baggenstoss⁵ three were due to periarteritis nodosa. Mucosal ulcerations, hemorrhage and secondary perforation and peritonitis were noted. One of the thirty patients described by Wold and Baggenstoss 16 had hemorrhagic ulcers and necrosis in the colon and rectosigmoid, while two of those of Johnson and Baggenstoss⁵ presented ulcers of the small bowel. Knowles et al.6 reported hemorrhage and/or ulcerations in the jejunum and colon in fifteen of thirty-five cases of periarteritis nodosa. Jernstrom and Stasney⁴ reported a fatal instance of periarteritis nodosa with ulceration of the stomach, ileum and colon found at necropsy. The rectum was not found to be ulcerated; the antemortem sigmoidoscopic appearance. however, of "diffuse redness and granularity," with blood tinged mucus was considered "suggestive of non-specific ulcerative colitis." Utilizing a telescopic device and a green filter, Felsen² first described certain sigmoidoscopic findings in periarteritis nodosa. He noted "linear, dark red streaks" followed by a "bloodless hairline" without necrosis or inflammation of the mucosa, and he interpreted these to be thrombosed submucosal arteries. The appearance of the mucosa through the sigmoidoscope, however, is generally not diagnostic.

A somewhat different clinical picture is presented by allergic granulomatous angiitis. It consists of asthma, blood eosinophilia, fever, Loeffler's pneumonia, and vascular occlusions and their sequelae. Churg and Strauss¹ reviewed the clinical and pathologic features of fourteen

742

patients. They noted that "abdominal pain and diarrhea, often bloody," were present in almost every case. In the gastrointestinal tract the pathologic findings consisted primarily of infarction, hemorrhage and scar formation. The prognosis is somewhat better in this form of arteritis but heart failure is a frequent terminal mechanism. Our patient fulfills the clinical criteria of this entity since he has had asthma with bouts of fever and marked eosinophilia, Loeffler's pneumonia, skin and central nervous system involvement. We believe, therefore, that he is suffering from allergic granulomatous angiitis.

For approximately six years prior to the appearance of those symptoms that can be ascribed to this vascular disorder, this patient had had symptoms of a serious colonic disease. These symptoms have continued to the present writing. The clinical course of this aspect of his illness and the x-ray and sigmoidoscopic examinations demonstrated the existence of chronic idiopathic ulcerative colitis. Nothing has been found in the prolonged study of this patient to distinguish his colonic disease from that of others in whom a diagnosis of chronic ulcerative colitis has been accepted.

In seeking an explanation for the occurrence of necrotizing angiitis in a patient with ulcerative colitis, consideration must be given to the following possibilities: (1) The same etiologic factor, as yet unknown, may result in the development of necrotizing angiitis and ulcerative colitis. (2) Necrotizing angiitis may be the original disease and may result in gastrointestinal lesions and a clinical picture which superficially resemble chronic ulcerative colitis. (3) Necrotizing angiitis may be a result of attempts at therapy of chronic ulcerative colitis, particularly with sulfonamides, amebicides, etc. (4) The appearance of the two diseases in the same patient may be entirely coincidental.

Since so little is known concerning the etiology and pathogenesis of both chronic ulcerative colitis and necrotizing angiitis, it is impossible to state they may not have a common cause. It is believed by some that necrotizing angiitis is to be grouped with lupus erythematosus, rheumatic fever, dermatomyositis, scleroderma, rheumatoid arthritis and allergic purpura under the inclusive term "collagen disease." Levine, Kirsner and Klotz, basing their opinion on a special study of the connective tissue of colons of patients with ulcerative colitis, have suggested that ulcerative colitis may also be a disease of

this category. Warren and Sommers, 14,15 noted that the lesions of the blood vessels in ulcerative colitis of their "vasculitis type" were similar to those seen in periarteritis nodosa. It is not unusual for patients with ulcerative colitis to have extracolonic manifestations of their disease—arthralgia, skin lesions such as pyoderma, gangrenosum and erythema nodosum—that are similar to those encountered in necrotizing angiitis. 3,9,13 A common background for both ulcerative colitis and necrotizing angiitis must, therefore, be conceded to be a possibility.

Because this patient had had all the characteristic features of chronic ulcerative colitis for so long before any manifestations of angiitis appeared, it seems quite unlikely that angiitis could be considered to have produced the colonic disease. In addition, the involvement of the entire colon and the nature of the sigmoidoscopic changes seem much more suggestive of the existence of idiopathic ulcerative colitis than of the gastrointestinal changes which have been reported to occur in necrotizing angiitis.

Lesions identical with those of periarteritis nodosa can be produced in animals by a number of technics. Studies of the experimental production of arterial lesions and of the pathologic correlation of similar lesions in man have emphasized the factor of hypersensitivity. The necrotizing angiitides have been seen to develop after the administration of drugs, particularly the sulfonamides. 6,17,18 More et al. 10 studied postmortem material in 375 patients who had taken sulfonamides and found lesions attributable to the drugs in twenty-two. Rich11,12 implicated sulfonamides, serum and the general role of hypersensitivity in the etiology of necrotizing angiitis. Zeek^{17,18} also believed these factors, particularly sulfonamides, to be important in causing angiitis. Most patients with ulcerative colitis are given sulfonamides and a few are given amebicides at some time in the course of their disease. Few seem to develop an obvious form of arteritis. We believe, however, that in the patient whom we have described the development of a form of necrotizing angiitis, allergic granulomatous angiitis, may well have been a result of the therapy he had received for chronic ulcerative colitis.

SUMMARY

A patient who has both chronic ulcerative colitis and allergic granulomatous angiitis is reported. The possible relationship of these

AMERICAN JOURNAL OF MEDICINE

diseases is discussed. It is suggested that treatment of ulcerative colitis with sulfonamides or amebicides may be of some etiologic significance in the subsequent development of necrotizing angiitis.

Acknowledgment: We wish to thank Doctors Nathan Blumberg, Henry Brody, Antonio Valdes-Dapena and Harold Israel for permission to utilize material relative to this case report.

REFERENCES

- Churg, J. and Strauss, L. Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am. J. Path., 27: 277-301, 1951.
- Felsen, J. The sigmoidoscopic diagnosis of periarteritis nodosa. Ann. Int. Med., 15: 251, 1941.
- GILMAN, R. L. and KAESS, K. V. Polyarteritis nodosa and dermatitis gangrenosa. Arch. Dermat. & Syph., 67: 184-186, 1953.
- Jernstrom, P. and Stasney, J. Acute ulcerative enteritis due to polyarteritis. J. A. M. A., 148: 544-546, 1952.
- Johnson, C. C. and Baggenstoss, A. H. Mesenteric vascular occlusion. Proc. Staff Meet., Mayo Clin., 24: 649–656, 1949.
- 6. Knowles, H. C., Jr., Zeek, P. M. and Blanken-Horn, M. A. Studies on necrotizing angiitis. IV. Periarteritis nodosa and hypersentitivity angiitis. Arch. Int. Med., 92: 789–805, 1953.
- 7. Kobernick, S. D. Experimental rheumatic carditis,

- periarteritis nodosa and glomerulonephritis. Am. J. M. Sc., 224: 329–342, 1952.
- Levine, M. D., Kirsner, J. B. and Klotz, A. P. A new concept of ulcerative colitis. Science, 114: 552, 1951.
- 9. McIver, M. A. and Lucas, S. V. Pyoderma gangrenosum. Surgery, 30: 573-577, 1951.
- MORE, R. H., McMILLAN, G. C. and DUFF, G. L. The pathology of sulfonamide allergy in man. Am. J. Path., 22: 703-725, 1946.
- Rich, A. R. The role of hypersensitivity in periarteritis nodosa. Bull. Johns Hopkins Hosp., 71: 123-140, 1942.
- Rich, A. R. Additional evidence of the role of hypersensitivity in the etiology of periarteritis nodosa. Bull. Johns Hopkins Hosp., 71: 375-379, 1942.
- SAMITZ, M. H. and GREENBERG, M. S. Skin lesions in association with ulcerative colitis. Gastroenterology, 19: 476-479, 1951.
- 14. WARREN S. and SOMMERS, S. C. Pathogenesis of ulcerative colitis. Am. J. Path., 25: 657-679, 1949.
- WARREN, S. and SOMMERS, S. C. Pathology of regional ileitis and ulcerative colitis. J. A. M. A., 154: 189-193, 1954.
- Wold, L. E. and Baggenstoss, A. H. Gastrointestinal lesions of periarteritis nodosa. *Proc. Staff Meet.*, Mayo Clin., 24: 28-35, 1949.
- 17. Zeek, P. M. Periarteritis nodosa: a critical review. Am. J. Clin. Path., 22: 777-790, 1952.
- 18. Zeek, P. M. Periarteritis nodosa and other forms of necrotizing angiitis. *New England J. Med.*, 248: 764-772, 1953.

Normal Bone Marrow in Untreated Pernicious Anemia*

Burton Cominsky, m.d.† and Catherine I. Holavko, a.b. New York, New York

The presence of a megaloblastic bone marrow is so characteristic of untreated pernicious anemia¹⁻⁶ that failure to demonstrate it by marrow aspiration may cast substantial doubt on the diagnosis. Recently, four patients with untreated anemia have been encountered whose routine marrow examinations showed no megaloblasts but whose clinical findings and response to therapy established the diagnosis of pernicious anemia. This point has perhaps escaped general notice and should be emphasized, especially since the patients concerned may have nervous system disease demanding early intensive therapy.

CASE REPORTS

CASE I. W. H. (No. 138853), a sixty year old retired industrial engineer, was admitted in May, 1953, complaining of "electric shocks" in his arms and legs and increasing difficulty in walking of two years' duration. He had been in good health until 1950 when he had bilateral calf thrombophlebitis and right epidydimitis. Since then he had experienced shooting sensations, like "electric shocks," down the anterior and lateral surfaces of both lower extremities, in the neck and down both arms. These "shocks" were increased in intensity by forward bending of the neck. Two years prior to admission he had had gradually increasing difficulty in walking, particularly in the dark. He had received no therapy.

Physical examination revealed a well developed, ruddy, white man with a wide-based, unsteady gait. The tongue was normal. Muscle strength was intact, with no atrophy or fasciculations. The Romberg sign was positive. No tremors were evident. Cranial nerves were

intact. The pupils were slightly irregular but reacted promptly to light and accommodation. There was marked diminution of vibratory and position senses in all four extremities, with preservation of pain and temperature sense. The heel-to-knee and down-shin test was poorly performed bilaterally. There were no Hoffmann or Babinski reflexes.

The hemoglobin was 14 gm.; red blood count 3.2 M; hematocrit 50 per cent; white blood count 5,300; platelets 206,000. Sternal bone marrow aspiration showed a normal active marrow. No megaloblasts were seen. Gastric analysis revealed no free acid after histamine. Spinal fluid showed normal pressures, was clear, contained one white blood cell and a protein of 60 mg. per cent. The colloidal gold and Wassermann tests were negative.

The serum Mazzini test was +, with Kolmer and Treponema pallidum immobilization tests negative. The cephalin flocculation test was negative. Bromsulfalein retention after thirty minutes was 12 per cent. Skull x-rays were normal. Roentgenograms of the spine revealed moderate osteoarthritic changes in the cervical, dorsal and lumbar regions. A gastrointestinal series showed a shortened esophagus with a small hiatus hernia.

On June 4, 1953, the patient began to receive $30~\mu g$. of vitamin B_{12} intramuscularly daily. His reticulocyte count rose from 1.3 per cent to a peak of 5 per cent on the sixth day of treatment. One month later the "shocks" in his extremities had virtually disappeared. By September, 1953, walking had improved and he no longer stumbled. He continued at times to experience pinsand-needles sensations in his wrists and in both legs from mid-calf down. The Romberg test was now negative; vibratory and position sense

^{*} From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y.
† Postdoctorate Research Fellow, U. S. Public Health Service.

were normal in both upper extremities but still absent below the knees bilaterally. His hemoglobin was 15.9 gm.; red blood count 4.1 M.

CASE II. U. F. (No. 122113), a seventy year old woman, was admitted May 25, 1953, complaining of unsteadiness of gait, pins-and-needles sensations in both lower extremities and in the left hand of five months' duration. She had previously been admitted in January, 1953, for an acute right calf thrombophlebitis. At that time the blood pressure was 180/80; there was a harsh aortic systolic murmur transmitted to the neck. The right calf was tense, swollen, red and warm. The remainder of the physical examination was normal. Hemoglobin was 13 gm.; hematocrit 38 per cent. She received anticoagulant therapy and bedrest. After discharge the patient experienced pins-and-needles sensations in both lower extremities and in her left hand, and her gait became unsteady. These symptoms gradually increased in intensity till readmission to the hospital in May, 1953. She received no treatment during this period. At this time physical examination was unchanged save that there were no signs of the previous thrombophlebitis.

On neurologic examination her gait was unsteady. Deep tendon reflexes in the arms were intact as were the superficial abdominal reflexes. Knee jerks and ankle jerks were absent. There were no pathologic reflexes. Vibratory and position senses were decreased in both lower extremities. Pain and temperature sense was intact. Cranial nerves and muscle strength were normal.

The hemoglobin was 12.3 gm.; red blood count 3.4 M; hematocrit 43 per cent; MCV 126; MCH 36; MCHC 28; white blood count 6,100. Bone marrow aspiration revealed a normal active marrow without megaloblasts. Gastric analysis showed no free acid after histamine. Spinal fluid was clear, showed normal pressures, contained one white blood cell and a protein of 36 mg. per cent. The colloidal gold and Wassermann tests were negative.

The serum Mazzini test was negative. X-rays of the spine revealed demineralization of the vertebrae, osteoarthritic changes in the cervical dorsal and lumbar regions, and a rotary scoliosis of the lumbar and dorsal spine.

Vitamin B_{12} , thirty μ g. intramuscularly daily, was started on May 29, 1953. Four days later the patient's reticulocyte count had risen from 0.4

per cent to a peak of 2.6 per cent. She was discharged to receive 15 μ g. of vitamin B₁₂ intramuscularly, three times a week. On June 23rd her hemoglobin was 13.4 gm. and her red blood count 4.2 M. Her paresthesias had decreased, but walking was still poor. By September 22, 1953, she was walking well, paresthesias had disappeared and position and vibratory senses were normal. The hemoglobin was 13.9 gm.; red blood count 4.2 M.

CASE III. C. B. (No. 125271), a sixty year old Negro housewife, was first seen in January, 1953, complaining of numbness and coldness of her legs and pins-and-needles sensations in her hands of two months' duration. In August, 1952, because of anorexia and weakness, she saw her local physician. Although blood counts are said to have been normal, she appeared anemic and was given liver and vitamin injections and ferrous sulphate. Her symptoms disappeared and treatment was stopped. By November, 1952, her symptoms returned and in addition she developed small ulcerations on her tongue and buccal mucous membranes. At that time her hemoglobin was 9.5 gm.; red blood count 3 M. She received liver and vitamin B₁₂ injections and ferrous sulphate, and although the lesions in her mouth cleared, she continued to feel weak and noted numbness and coldness of her legs, and pins-and-needles sensations in her hands. Her gait was normal.

Physical examination in January, 1953, revealed a well developed Negro woman. Her tongue and oral mucous membranes were normal. The thyroid gland was somewhat enlarged and nodular. No bruit was heard over the gland. There was diminished vibratory sense in both lower extremities; position sense was intact. Deep tendon reflexes were intact and no pathologic reflexes were present. The rest of the physical was negative.

The hemoglobin was 12.2 gm. The serum Mazzini test was negative. Stool guaiacs were negative. Radioactive iodine uptake was 36 per cent in twenty-four hours.

The patient was advised to stop her liver and vitamin injections and iron. In March, 1953, her symptoms were unchanged. The hemoglobin was 12.3 gm.; red blood count 4.25 M. When seen in June, 1953, she complained of numbness in both lower extremities and hands. Now the hemoglobin was 9.8 gm. and red blood count 2.6 M. She had received no treatment since

January, 1953. The patient was admitted to the hospital in July, 1953. Physical examination was unchanged and neurologic examination was normal.

Gastric aspiration revealed no free acid after histamine. A spinous process bone marrow aspiration on July 21, 1953, revealed a normoblastic marrow. No megaloblasts were seen. The patient received 100 µg. of vitamin B₁₂ intramuscularly on July 25th, and 15 μ g. weekly since. Her reticulocyte count rose from 1.6 per cent to a peak of 3.6 per cent six days after onset of therapy. By September, 1953, she no longer had any symptoms. The hemoglobin was now 13.6 gm.; red blood count 4.1 M.

Case IV. A. N. (No. 129016), a forty-six year old housewife, was admitted in February, 1953, complaining of difficulty in walking of seven months' duration. For seven months prior to admission the patient had experienced numbness and stiffness of both legs, difficulty in walking and transient numbness of her fingers. She had

received no therapy.

The patient was a well developed woman. Physical examination revealed weakness of both lower extremities below the knees, absent ankle jerks, bilateral Babinski reactions, impaired position sense and absent vibratory sense of both lower extremities. The hemoglobin was 10.9 gm.; red blood count 3.0 M; hematocrit 37 per cent; MCV 122; MCH 36; MCHC 30; white blood count 5,500; platelets 217,000. Bone marrow aspiration revealed no megaloblasts. There was no free acid on gastric analysis after histamine. One stool guaiac was ++, three others were negative. Stool for ova and parasites was negative. The serum Mazzini test was negative. Radioactive iodine uptake was 39 per cent in twenty-four hours. The cephalin flocculation test was +++. There was no retention of bromsulfalein after thirty minutes. The serum alkaline phosphatase was 2.2 Bodansky units. A gastrointestinal x-ray series was normal.

On February 25, 1953, the patient was started on a regimen of vitamin B₁₂, 60 µg. intramuscularly daily. Seven days later her reticulocyte count had gone from 0.2 per cent to a peak of 3.7 per cent. On March 4, 1953, the hemoglobin was 12.9 gm. The patient was discharged to receive 50 µg. of vitamin B₁₂ three times a week. By July, 1953, her walking had improved considerably and she no longer had numbness of her fingers. In October, 1953, position sense had improved but was still impaired, and

vibratory sense was now appreciated down to both malleoli. Hemoglobin was 16 gm.; red blood count 5.5 M.

COMMENTS

It is said that, in general, with lesser degrees of anemia the marrow is correspondingly less hyperplastic and fewer erythroblasts and megaloblasts are present.4 There are, however, few reports of the bone marrow changes that may be met in the face of minor degrees of anemia. In anemia of a degree perhaps comparable to that seen in the patients presented here, Dameshek and Valentine report that about 25 to 35 per cent of marrow cells are likely to be megaloblasts.4

Neurologic disturbances as part of pernicious anemia may be present in the face of slight anemia. Conley and Krevans⁷ have reported on two such patients in whom the bone marrow was normal. However, their patients had been treated beforehand with vitamin preparations, including folic acid, and the interpretation of the finding of a normal marrow is open to question. The four patients now reported all denied specifically the use of vitamin preparations.

SUMMARY

Bone marrow aspirations of four patients with pernicious anemia in relapse failed to reveal megaloblasts. Three of the four patients had nervous system disease. Awareness of the possibility of encountering normal marrow in pernicious anemia in relapse is important, especially because the patients may have, with minor degrees of anemia, neurologic disease that requires early intensive treatment.

REFERENCES

1. WINTROBE, M. M. Clinical Hematology. Philadelphia, 1952. Lea & Febiger.

2. CASTLE, W. B. and MINOT, G. R. Pathological Physiology and Clinical Description of the Anemias. London, 1936. Oxford University Press.

3. Peabody, F. W. The pathology of the bone marrow in pernicious anemia. Am. J. Path., 3: 179, 1927.

- 4. Dameshek, W. and Valentine, E. H. The sternal marrow in pernicious anemia. Arch. Path., 23: 159,
- 5. Jones, O. P. Morphologic, physiologic, chemical and biological distinction of megaloblasts. Arch. Path., 35: 752, 1943.

6. THADDEA, S. and SAUERBRUCH, F. Über besondere Verlaufsformen der perniziösen Anämie. Folia haematol., 61: 289, 1939.

7. Conley, C. L. and Krevans, J. R. Development of neurologic manifestations of pernicious anemia during multivitamin therapy. New England J. Med., 245, 529, 1951.

AMERICAN JOURNAL OF MEDICINE



Vallestril insures
maximal estrogenic
potency with
minimal activity on
the endometrium
and thus singular
freedom from
withdrawal bleeding.

Unique "Target Action" of Vallestril®

Vallestril has been found to exert its selective "target action" on the vaginal mucosa. Conversely the effect on the uterus or endometrium is negligible.

In pharmacologic studies, using the Allen-Doisy technic, Vallestril was found to be more active than estradiol and twice as potent as estrone on the vaginal mucosa. On the other hand, using the Rubin technic, Vallestril was found to have only one-tenth the activity of estrone on the uterus, a suggested explanation of its low incidence of withdrawal bleeding.

In clinical evaluation, covering a period of two and one-half years, Vallestril was found* to be "an effective synthetic estrogen . . . singularly free from toxic effects and complications, especially uterine bleeding.... The beneficial effect of the medication appeared within three or four

days in most menopausal patients....failure to encounter withdrawal bleeding in any patient was most gratifying...."

Such unwanted reactions as nausea, mastalgia and edema also occur less frequently with Vallestril.

Vallestril is preferentially indicated whenever estrogens are of value: The menopausal syndrome; pain of postmenopausal osteoporosis; pain of osseous metastases of prostatic cancer.

Dosage: Menopause—3 mg. (1 tablet) two or three times daily for two or three weeks, followed by 3 or 6 mg. daily for one month. Supplied only in scored tablets of 3 mg. G. D. Searle & Co., Research in the Service of Medicine.

^{*}Sturnick, M. I., and Gargill, S. L.: New England J. Med. 247:829 (Nov. 27) 1952.



IN THE COMMON COLD...

Prompt Symptomatic Relief with

Multihist*APC

MULTIPLE ANTIHISTAMINE .
ANALGESIC . ANTIPYRETIC

The state of the s

Taken at the onset of symptoms, Multihist + APC quickly suppresses the troublesome rhinorrhea of the common cold and relieves such general symptoms as headache, backache, and other discomfort. Each capsule provides 15 mg. of the Multihist combination (5 mg. each of Pyrilamine maleate, Prophenpyridamine maleate, and Phenyltoloxamine dihydrogen citrate) together with aspirin 3½ gr., phenacetin 2½ gr., and caffeine ½ gr. Because each antihistamine is provided in an amount virtually incapable of producing drowsiness or lethargy, the incidence of side effects is greatly reduced. Average dose, 2 capsules initially, followed by 1 capsule at 4-hour intervals. Available on prescription through all pharmacies.

SMITH-DORSEY

Lincoln, Nebraska
A Division of THE WANDER COMPANY

multiple
antihistamine
therapy means
reduced
incidence of
side effects

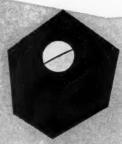
Combination tranquilizer-antihypertensive

especially for moderate and severe essential hypertension . . .

Serpasil-Apresoline®

hydrochloride

(RESERPINE AND HYDRALAZINE HYDROCHLORIDE CIBA)



Combined in a Single Tablet

- The tranquilizing, bradycrotic and mild antihypertensive effects of Serpasil, a pure crystalline alkaloid of rauwolfia root.
- The more marked antihypertensive effect of Apresoline and its capacity to increase renal plasma flow.

Each tablet (scored) contains 0.2 mg. of Serpasil and 50 mg. of Apresoline hydrochloride.

C I B A summit, N. J.

2/2051

wherever Codeine + APC is indicated

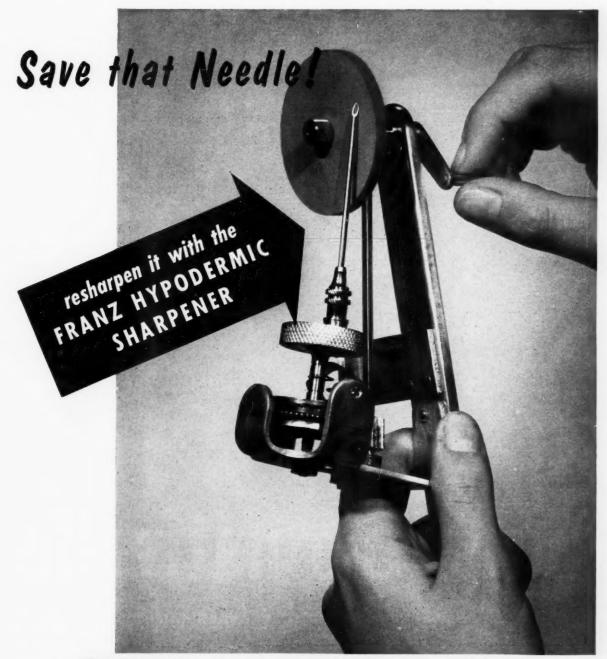
PERCODAN® TABLETS* FOR PAIN

Provides faster, longer-lasting, and more profound pain relief. Obtainable on prescription. Narcotic blank required.

*Salts of dihydrohydroxycodeinone and homatropine, plus APC.

ENDO PRODUCTS INC., Richmond Hill 18, N. Y.





HOSPITAL & INSTITUTIONAL TESTED

No special operating skill required . . . The skill is in the sharpener

Dulled needles, up to 2" in length, are accurately honed to precise sharpness in 6 seconds or less, with the Franz Hypodermic Sharpener.

It automatically puts the ideal point on your needles . . . you get sharp, clean edged needles that make inoculation easier for you — easier on your patients.

The sharpener may be held in the hand or permanently mounted on a desk or table.

Order your Franz Hypodermic Sharpener today—it will save you time, money and patients. The price is only \$24.95, postage paid.

53 Wallace Street New Haven, Conn.
Enclosed is check — M. O. fordollars. Please
send mesharpeners at \$24.95 each.
Name
Street
C'h.

FRANZ MFG. CO.

53 Wallace St.

New Haven, Conn.

compare before you prescribe

modern criteria of good digitalis therapy

- 1 pure active principle
- 2 complete absorption
- 3 rapid onset of action
- 4. smooth, even maintenance
- 5 frequent dosage readjustment unnecessary
- 6 virtual freedom from gastric upset

digitaline nativelle

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

compare then prescribe...

DIGITALINE NATIVELLE

—the original pure crystalline digitoxin

Consult your Physicians' Desk Reference for dosage information.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

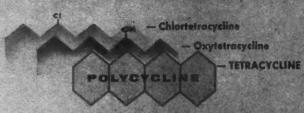
Thoroughbreds are born, not made—



3M A PRINT "HONORS EVEN" BY EDWIN MEGARGEE, NEW YORK, PUBLISMED & COPYRIGHTED 1943 BY FRANK J. LOWE.

POLYCYCLINE is the ONLY tetracycline produced directly by fermentation from a new species of Streptomyces isolated by Bristol Laboratories... rather than by the chemical modification of older antibiotics.

The most modern Broad-Spectrum Antibiotic



YCYCLIN



the only tetracycline produced directly by fermentation from a new species of Streptomyces isolated by Bristol Laboratories...rather than by the chemical modification of older broad-spectrum antibiotics.



effective in broad range

against gram-positive and gram-negative organisms.



less toxic

(lower incidence of side reactions) than older broad-spectrum antibiotics.



more soluble

than chlortetracycline (quicker absorption, wider diffusion).



more stable in solution

than chlortetracycline or oxytetracycline (higher, more sustained, blood levels).

Now available as

DLYCYCLINI SUSPENSION 250

(TETRACYCLINE Bristol)



-the ONLY oral suspension of tetracycline that is ready-to-use. Requires no reconstitution, no addition of diluent, no refrigeration—stable at room temperature for 18 months. Has appealing "crushed-fruit" flavor. Supplied in bottles of 30 cc., in concentration of 250 mg. per 5 cc.

Also available as POLYCYCLINE

CAPSULES

(TETRACYCLINE Bristol)

- 100 mg., bottles of 25 and 100. - 250 mg., bottles of 16 and 100.

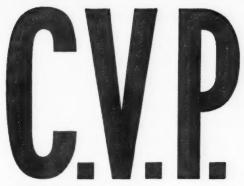


Dosage:

average adult, 1 gram daily, divided doses; children in proportion to body weight.



improve capillary resistance in prevention and treatment of capillary fragility capillary hemorrhage vascular accidents



(CITRUS FLAVONOID COMPOUND WITH VITAMIN C)

Five years of laboratory and clinical investigations establish the complete safety and value of C.V.P. in increasing capillary resistance and reducing abnormal bleeding due to capillary fragility.

C. V. P. provides natural bio-flavonoids (whole natural vitamin P complex) derived from citrus sources—potentiated by vitamin C—which act synergistically to thicken the intercellular ground substance (cement) of capillary walls, decrease permeability...and thus increase capillary resistance.

may protect against abnormal bleeding and vascular accidents in...

- hypertension
- retinal hemorrhage
- diabetes
- radiation injury
- purpura
- · tuberculous bleeding

"Many instances of hemorrhage and thrombosis in the heart and brain may be avoided if adequate amounts of vitamin P and C are provided."

each C.V.P. capsule provides:

Citrus Flavonoid Compound* 100 mg.

Ascorbic Acid (C)

100 mg.

*(water soluble whole natural vitamin "P" complex, more active than insoluble rutin or hesperidin)

Professional samples and literature on request.



bottles of 100, 500 and 1000 capsules



u. s. vitamin corporation

Arlington-Funk Laboratories, division 250 East 43rd Street, New York 17, N.Y.

NEW! C.V.P. SYRUP, pleasant tasting, especially useful to help prevent bleeding after tonsillectomy. Each 5 cc. (one teaspoonful) equivalent to one C.V.P. capsule.

NEW...council-accepted

oral anticoagulant

with a wide range of safety

(Brand of Phenindione, 2-phenyl-1, 3-indandione)



Permits dependable prothrombin control with little risk of dangerous fluctuations

- HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance
- HEDULIN is rapidly excreted—therapeutic effect dissipated within 24-48 hours if withdrawal becomes necessary
- HEDULIN acts promptly, producing therapeutic prothrombin levels in 18-24 hours
- HEDULIN requires fewer prothrombin determinations only one in 7 to 14 days, after maintenance dose is established
- HEDULIN's anticoagulant action is rapidly reversed by vitamin K₁ emulsion

DOSAGE: 4 to 6 tablets (200 to 300 mg.) initially, half in the morning and half at night; maintenance dosage (on basis of prothrombin determinations daily for first three days), 50 to 100 mg. daily, divided as above.

Available on prescription through all pharmacies, in original bottles of 100 and 1000 50-mg. scored tablets.

Complete literature to physicians on request



Walker LABORATORIES, INC., MOUNT VERNON, N. Y.

*Registered trademark of Walker Laboratories, Inc.



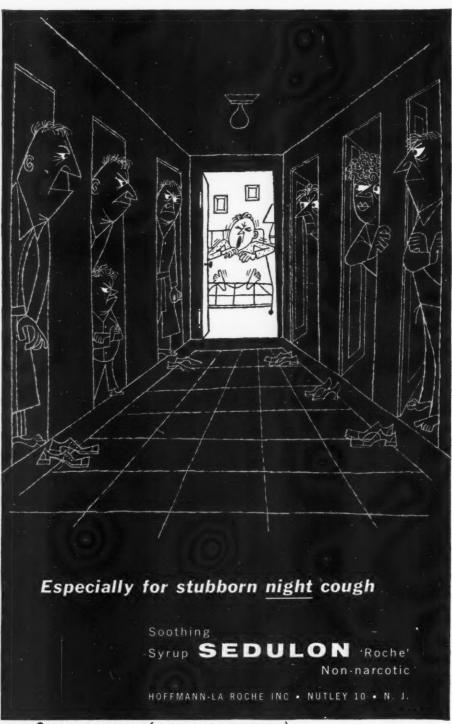
Doctor, do you feel that your colleagues are missing important new medical findings by not reading The American Journal of Medicine?

Let us send them a complimentary copy—of course there is no obligation to you or your colleagues. Just fill out the coupon and mail it to us.

Dr	Dr
Address	
Dr	Your Name
Address	Address
	AIM

The American Journal of Medicine

49 West 45th Street, · New York 36, New York



SEDULON® .- BRAND OF DIHYPRYLONE (3,3-DIETHYL-2,4-DIOXO-PIPERIDINE)

In Myocardial Infarction

C·R·P·A*

C-Reactive-Protein Antiserum - Schieffelin

A highly sensitive test for presence of inflammation

- Investigators have found this test to be consistently negative in cases of cardiac insufficiency uncomplicated by myocardial infarction and inflammation.^{1,4}
- based upon presence of specific C-reactive protein in serum of patients with certain inflammatory diseases — characteristic precipitin reaction develops upon addition of C·R·P·A to serum of such patients . . . C-reactive protein is never found in normal serum.²
- simple, economical, routine laboratory procedure that has been demonstrated to be the most consistently positive test in the presence of rheumatic activity³... often reveals presence of subclinical inflammatory reactions... detects relapse or recurrence of inflammatory disease... and aids in gauging adequacy of therapeutic regimens.
- *False positive tests do not occur since CRP is not present, even in trace amounts, in normal sera" . . . accurate qualitative reading may be made within 30 minutes . . . preliminary quantitative estimate obtained within 2 hours.

For detailed instructions on the materials and techniques required for the use of C·R·P·A — Schieffelin, just send us a request and we will mail you a descriptive brochure.

- 1. Kroop, I. G. and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95 (May) 1954.
- 2. Wood, H. F., and McCarty, M.: J. Clin. Investigation 30:616 (June) 1951.
- 3. Stollerman, G. H., et al.: Am. J. Med. 15:645 (Nov.) 1953.

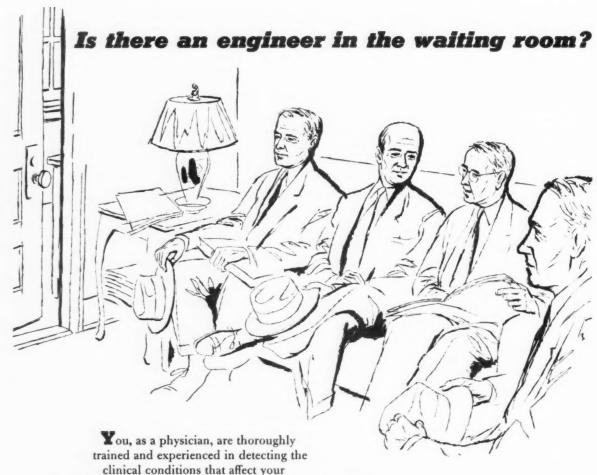
4. Hedlund, P.: Acta med. Scandinav., Supplement 196:579, 1947.

Supplied: 1 cc. vials (30-40 determinations)

Schieffelin & Co., Pharmaceutical and Research Laboratories since 1794
18 Cooper Square, New York 3, N.Y.

*trademark





patients' physical being. They depend on you completely for a knowledge and guidance not possessed by themselves. Conversely, do you not similarly look to professional men in other fields for aid when the need arises?

For example, when there's the question of quality in the consideration of a new piece
of diagnostic equipment – such as an electrocardiograph –
an engineer can tell better than anyone, sometimes with just a superficial examination,
how well the instrument is designed and made. He notices such things
as workmanship, the quality of materials, and the grade of the components. As an engineer
he would be sure to see the value in unitized construction in the Viso-Cardiette –
amplifier, control panel and recorder as three basic assemblies –
and the advantages of inkless recording in true rectangular coordinates.
He would remark about the minimum of moving parts, the ruggedness
of construction, and the precision instrument quality
of the purchased components.

This EXCLUSIVE plan places a Viso-Cardiette in your hands for 15 days. At the end of that trial period, if you are not completely satisfied with the instrument, you simply return it to us and that is all! You're under NO OBLIGATION.

If you are trying to decide which electrocardiograph to buy, we invite this type of comparison between the Viso-Cardiette and any other instrument. To make such an examination of the Viso possible, you may have a Viso for a 15-day trial* without any obligation whatsoever.

SANBORN COMPANY

Cambridge 39, Massachusetts

an advance in therapy of adrenocortical insufficiency

Percorten trimethylacetate

intramuscular repository

"A month's therapy with a single injection." Therapy of chronic adrenocortical insufficiency has been improved and made more convenient to both patient and physician by Ciba's introduction of Percorten trimethylacetate in the form of a long-acting microcrystalline suspension. ¹⁻⁵ • A single injection of this new long-acting steroid hormone derivative provides maintenance therapy for about a month. • This protracted and constant therapeutic effect is achieved because the suspension, when administered by deep intramuscular injection, simulates a miniature pellet in that a small fraction of the total dose is absorbed daily. • Patients who have Addison's disease and who are not in crisis can now be treated on a highly satisfactory ambulatory basis.

Indications: Chronic primary and secondary adrenocortical insufficiency, and hypotension associated with adrenal insufficiency. Supplied: Multiple-dose vials—4 ml. containing 25 mg. ml. as an aqueous suspension for intramuscular use only. Note: Percorten (desoxycorticosterone Ciba) is available in 4 administration forms: (1) Percorten trimethylacetate, long-acting intramuscular repository, aqueous suspension; (2) Percorten acetate in oil solution, for intramuscular injection; (3) Percorten acetate Linguets, for sublingual or parabuccal absorption; (4) Percorten acetate pellets, for subcutaneous implantation.

Ask your Ciba professional service representative or write the Medical Service Division for complete information on the use of Percorten trimethylacetate.

1. Gross, F., and Tschopp, E.: Experientia 8:75, 1952. 2. Thorn, G. W., and Jenkins, D.: In press. 3. Thorn, G. W.; Jenkins, D.; Arons, W. L., and Frawley, T. F.: Schweiz. med. Wchnschr. 82:697, 1952. 4. Gaunt, R.; Leathem, J.; Howell, C., and Antonchak, N.: Endocrinology 50:521, 1952. 5. Sorkin, S. Z., and Soffer, L. J.: Am. Fed. Clin. Research, May 4, 1952.

Ciba Summit, New Jersey

2/1916M

24-hour control

for the majority of diabetics



GLOBIN INSULIN 'B.W. & CO.'

a clear solution . . . easy to measure accurately

Discovered by Reiner, Searle, and Lang in The Wellcome Research Laboratories



broad-spectrum antibiotic

Tetracyn*

For well-tolerated therapy of such common infections as:

Pneumococcal infections, including pneumonia, with or without bacteremia; streptococcal infections. with or without bacteremia, including follicular tonsillitis, septic sore throat, scarlet fever, pharyngitis, cellulitis, urinary tract infections due to susceptible organisms, and meningitis; many staphylococcal infections, with or without bacteremia. including furunculosis, septicemia, abscesses, impetigo, acute otitis media, ophthalmic infections, susceptible urinary tract infections, bronchopulmonary infections, acute bronchitis, pharyngitis, laryngotracheitis, tracheobronchitis, sinusitis, tonsillitis, otitis media, and osteomyelitis; certain mixed bacterial infections; soft tissue infections due to susceptible organisms.

Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., world's largest producer of antibiotics, discoverers of oxytetracycline and the first to describe the structure of tetracycline, nucleus of modern broad-spectrum antibiotic therapy.

Tetracyn is supplied as Capsules,
Tablets, Oral Suspension (chocolate
flavored), Pediatric Drops (banana
flavored), Intravenous, Intramuscular,
Ophthalmic Ointment, and Ointment
(topical).

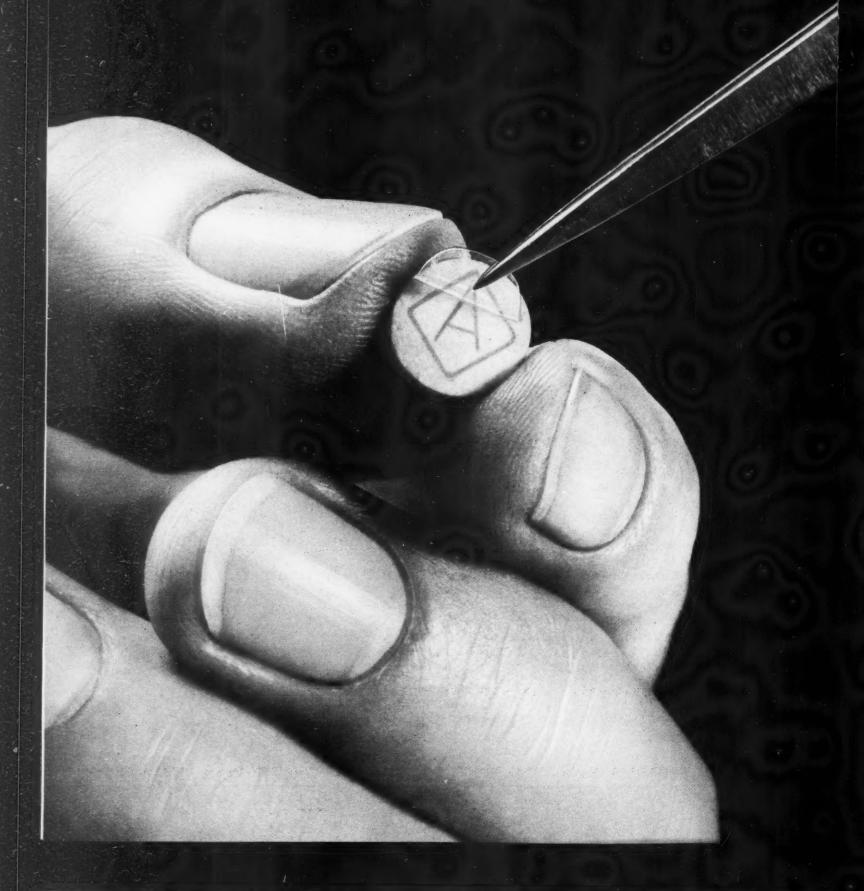
#TRADEMARK



PFIZER LABORATORIES, Brooklyn 6, N. Y. Division, Chas. Pfizer & Co., Inc.

the coating so thin
you can almost peel it...

high blood levels...



...in 2 hours or less



Erythromycin Stearate, Abbott) Representation of the Stearate of the Stearate

disintegrates faster than enteric-coated erythromycin

TISSUE-THIN FILMTAB COATING (marketed only by Abbott) actually starts to dissolve within 30 seconds after administration—makes Erythrocin available for immediate absorption.

Tests show that new Stearate form definitely protects

Erythrocin from gastric juices.

BECAUSE THERE'S NO DELAY FROM AN ENTERIC COATING, your patient gets high, inhibitory blood levels within 2 hours—instead of 4-6 as before. Peak concentration at 4 hours, with significant levels for 8 hours.

use filmtab erythrocin stearate against the cocci... and especially when the organism is resistant to other antibiotics. Low in toxicity—it's less likely to alter normal intestinal flora than most oral antibiotics. Conveniently sized (100 and 200 mg.) in bottles of 25 and 100.

*TM for Abbott's film sealed tablets, pat. applied for

rauwolfia
in its

optimal
form
typ

- Rauwiloid is not the crude rauwolfia root. Rauwiloid presents the total hypotensive activity of the pure whole Rauwolfia serpentina (Benth.) root—but it is freed from the inert dross of the whole root and its undesirable substances such as yohimbine-type alkaloids.
- Rauwiloid is not merely a single contained alkaloid of rauwolfia. Rauwiloid provides the balanced action of the several potent alkaloids in rauwolfia; reserpine—regardless of the brand name under which it is marketed—is only one of the desirable alkaloids in Rauwiloid.
- Rauwiloid contains, besides reserpine, other active alkaloids, such as rescinnamine, 1.2 reported to be more potent than reserpine.
- Rauwiloid is the original alseroxylon fraction of unadulterated Rauwolfia serpentina (Benth.)—rauwolfia in its optimal form—virtually no side actions—no known contraindications. It rarely needs dosage adjustment. The dose for most patients is 2 tablets (2 mg. each) at bedtime.

If you have prescribed rauwolfia in other forms, it will not take many patients to convince you that Rauwiloid serves better. Please write for clinical samples.

IN HYPERTENSION

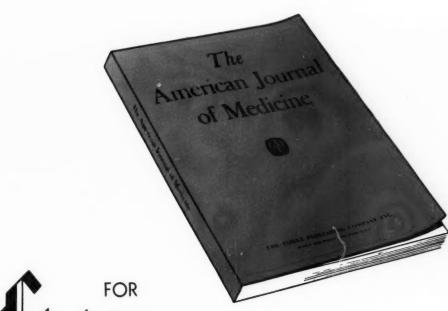
Rauwiloid



LABORATORIES, INC. LOS ANGELES 48, CALIF.

Klohs, M. W.; Draper, M. D., and Keller, F.: J. Am. Chem. Soc. 76:2843 (May 20) 1954.

^{2.} Cronheim, G.; Brown, W.; Cawthorne, J.; Toekes, M. I., and Ungari, J.: Proc. Soc. Exper. Biol. & Med. 86:110 (May) 1954.



Thristmas. THE IDEAL GIFT FOR YOUR COLLEAGUE OR DOCTOR FRIEND

An up-to-date medical journal any doctor will take pride in having in his library—beautifully printed and illustrated—a publication that will provide both pleasure and inspiration.

The American Journal of Medicine
49 West 45th St.

New York 36

Yearly Subscription \$12.00 U.S.A.

Canada \$13.00

Foreign including Latin-American Countries \$15.00



ELECTRON PHOTOMICROGRAPH

Diplococcus pneumoniae 35,000 x

Diplococcus pneumoniae (Streptococcus pneumoniae) is a Gram-positive organism commonly involved in

lobar—and bronchopneumonia • chronic bronchitis • mastoiditis • sinusitis otitis media • and meningitis.

It is another of the more than 30 organisms susceptible to

PANMYCIN

100 mg. and 250 mg. capsules

TRADEMARK, REG. U. S. PAT. OFF.

Upjohn

Through its three-fold action in arthritis...relief of pain, improvement of function, and resolution of inflammation... BUTAZOLIDIN contributes significantly to the rehabilitation of the arthritic patient.

In addition to its marked therapeutic effectiveness, the advantages of BUTAZOLIDIN include:

Wide Scope of Usefulness-effective in the most crippling and chronic arthritides.

Persistence of Effect-does not provoke tolerance on continued usage.

Nonhormonal in Character- the therapeutic action of BUTAZOLIDIN is not mediated through the pituitary-adrenocortical axis.

BUTAZOLIDIN being a potent agent, the physician should carefully select candidates for treatment and promptly adjust dosage to the minimal individual requirement. Patients should be regularly examined during treatment, and the drug discontinued should side reactions develop.

Detailed literature on request.

BUTAZOLIDIN® (brand of phenylbutazone): Red sugar-coated tablets of 100 mg.

in arthritis and allied disorders

BUTAZOLIDIN°



nonhormonal anti-arthritic

relieves pain . improves function . resolves inflammation



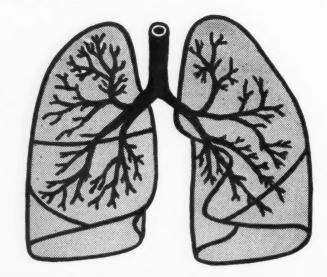


GEIGY PHARMACEUTICALS Division of Geigy Chemical Corporation 220 Church Street, New York 13, N. Y. In Canada:

Geigy Pharmaceuticals, Montreal

Symposium

on RECENT ADVANCES in the DIAGNOSIS and MANAGEMENT of . . .



BRONCHOPULMONARY

DISEASES

Rarely in surgical journalism is it possible to obtain so complete and authoritative a compendium so conveniently. Under the guest editorship of Emil A. Naclerio, M.D., F.C.C.P., THE AMERICAN JOURNAL OF SURGERY dedicates its January and February 1955 issues to this timely Symposium dealing with advances in the diagnosis and management of bronchopul-monary diseases. A glance at the contents of this Symposium should convince you of its all-inclusiveness and value for quick reference in all medical and surgical aspects of Bronchopulmonary Disease.

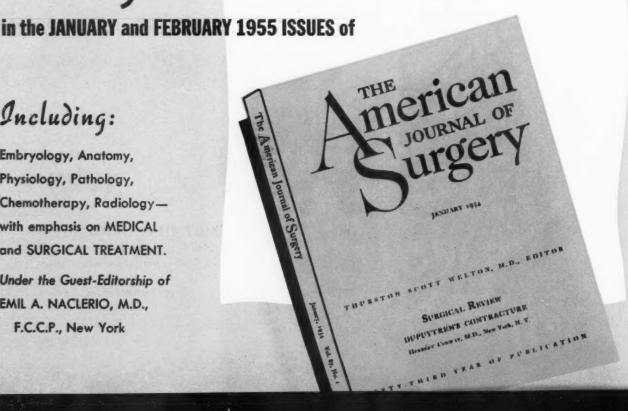
Purchased separately these two Symposium Issues cost \$8.00. Your year's subscription to The American JOURNAL OF SURGERY, beginning with the January and February issues, will bring you not only this important Symposium but ten additional issues of this practical surgical journal for only \$7.00 more. Act now to make these Symposium Issues available for your own ready reference and study. Fill out and mail today the subscription order form on opposite page.

Coming.

Including:

Embryology, Anatomy, Physiology, Pathology, Chemotherapy, Radiologywith emphasis on MEDICAL and SURGICAL TREATMENT.

Under the Guest-Editorship of EMIL A. NACLERIO, M.D., F.C.C.P., New York





Partial Contents by Title and Author

Agenesis of the Lung A. R. Valle, Washington, D. C. **Developmental Anomalies of the Lungs** Edward A. Boyden, Minneapolis, Minn. Functional Anatomy of the Lung Leroy D. Vandam, Boston, Mass. Hematologic Role of the Lung Howard R. Bierman, Duarte, Calif. Physiology of Respiration Hurley L. Motley, Los Angeles, Calif. Management of Impaired Respiratory Function James L. Whittenberger, Boston, Mass. Pathology of Tuberculosis as Affected by Antibiotics Oscar Averbach, East Orange, N. J. Pathology of Pulmonary Disease David M. Spain, Brooklyn, N. Y. Role of Cytology in Diagnosis of Primary **Bronchogenic Carcinoma** John R. McDonald, Rochester, Minn. Home Management of Pulmonary Tuberculosis Donald R. McKay, Buffalo, N. Y. Present Status of Pneumotherapy in Management of Pulmonary Tuberculosis James H. Cullen, Albany, N. Y. Segmental Resection in Pulmonary Tuberculosis J. Maxwell Chamberlain, New York, N. Y. Cancer of the Lung Richard H. Overholt, Brookline, Mass. Treatment of Allergies of the Respiratory Tract Joseph Harkavy, New York, N. Y. Viral Diseases of the Chest A. F. Rasmussen, Jr., Los Angeles, Calif. Collagen Disease L. Henry Garland, San Francisco, Calif. **Pneumoconioses** Arthur J. Vorwald, Detroit, Mich. Coccidioidomycosis Bert H. Cotton, Los Angeles, Calif. Beryllium Poisoning, X-ray Manifestations and **Advances in Treatment** H. E. Tebrock, New York, N. Y. Spontaneous Pneumothorax John N. Briggs, Los Angeles, Calif. **Bronchiectasis** Francis M. Woods, Brookline, Mass. Benign Tumors of the Bronchus and Lungs Lew A. Hochberg, Brooklyn, N. Y. Cystic Disease of the Lung Jerome R. Head, Chicago, III. Lesions of Lung in Lymphomatoid Disease Henry D. Diamond, New York, N. Y. Penetrating Wounds of the Lung Del Aubre Maynard, New York, N. Y. Pulmonary Embolism and Infarction Irving S. Wright, New York, N. Y. Smoking in Relation to Lung Cancer William L. Watson, New York, N. Y.

12 ISSUES . . . \$15.00

Two symposium issues
ordered separately . . . \$8.00
Full Year Subscription gives you
10 additional issues for only \$7.00 more.

Cancer of the Lung John H. Gibbon, Jr., Philadelphia, Pa. Effect of Pulmonary Disease on the Heart Maxwell L. Gelfand, New York, N. Y. Cardiac Arrest during Pulmonary Resection Julian Johnson, Philadelphia, Pa. **Pulmonary Complications of Heart Disease** N. E. Reich, Brooklyn, N. Y. Metastases to the Lung from Breast Carcinoma Frank Adair, New York, N. Y. Treatment of Inoperable Pulmonary Cancer David A. Karnofsky, New York, N. Y. Fundamental Considerations in Chemotherapy of **Acute Pneumonias** Paul A. Bunn, Syracuse, N. Y. ACTH and Cortisone in Respiratory Diseases Maurice S. Segal, Boston, Mass. Current Status of Antimicrobial Agents in the Treatment of Pulmonary Tuberculosis Nicholas D. D'Esopo, West Haven, Conn. Roentgen Differential Diagnosis of Pulmonary Disease Noel F. Bartone, New York, N. Y. Reliability of Chest Radiography in Diagnosis of Pulmonary Lesions J. Yerushalmy, Berkeley, Calif. Bronchography in Pulmonary Disease
Arthur Cracovoner, New York, N. Y. Radioisotopes in Pulmonary Disease Bernard Roswit, Bronx, N. Y. Anesthesiology in Pulmonary Surgery John S. Lundy, Rochester, Minn. Effect of Pulmonary Disease in Inhalation Anesthesia Joseph G. Giuffrida, Brooklyn, N. Y. Use of Exsufflation in Pulmonary Disease Alvan L. Barach, New York, N. Y. Pre- and Postoperative Management in Pulmonary Surgery Victor Richards, San Francisco, Calif. Indications for Pulmonary Resection Emil A. Naclerio, New York, N. Y. Use of Pedicled Pericardial Fat Graft in Resection Lyman A. Brewer, Los Angeles, Calif. **Pulmonary Decortication** Paul C. Samson, Oakland, Calif. Segmental Bronchi and Bronchopulmonary Segments Chevalier L. Jackson, Philadelphia, Pa. Preservation of Lung Tissue Donald L. Paulson, Dallas, Tex. Postoperative Complications in Pulmonary Surgery

and 40 other articles

SUBSCRIPTION ORDER FORM

Selection of Patients with Pulmonary Disease for Air Travel

Rehabilitation in Thoracic Surgery

Otto C. Brantigan, Baltimore, Md.

Burgess Gordon, Philadelphia, Pa.

Albert Haas, New York, N. Y.

T		can Journal	0 0 .
	starting with the J JOURNAL OF SU	subscription for on anuary, 1955, issue RGERY. Subscription 6.00; foreign, \$17.	to THE AMERICAN U.S.A., \$15.00 per
	Please send me \$4.00 each.	the January and	February issues at
NAM	E		
ADDR	RESS	-	
CITY		ZONE	STATE



Sample Of

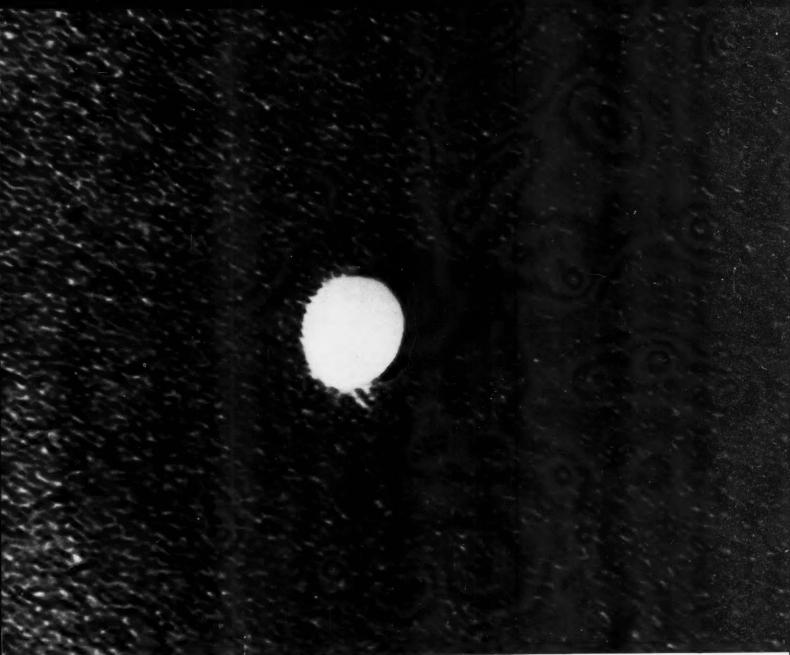
Obedrin

E. MASSENGILL CO.

Bristol, Tennessee

viated.

of impaction caused by "bulk" producers is ob-



ELECTRON PHOTOMICROGRAPH

Staphylococcus aureus 35,000 x

Staphylococcus aureus (Micrococcus pyogenes var. aureus) is a Gram-positive organism commonly involved in a great variety of pathologic conditions, including pyoderma • abscesses • empyema • otitis • sinusitis • septicemia bronchopneumonia • bronchiectasis • tracheobronchitis • and food poisoning.

It is another of the more than 30 organisms susceptible to

PANMYCIN

100 mg. and 250 mg. capsules

Upjohn

PROFOUND RELIEF AND QUICK REHABILITATION

IN acute bursitis

Profound and rapid therapeutic success in bursitis, especially in the acute stage, is obtained with HP*ACTHAR Gel. Cases refractory to other types of therapy have responded to HP*ACTHAR Gel, regardless of the severity of the condition. Calcium deposits may disappear.

HP*ACTHAR Gel, a new repository ACTHAR with rapid response and sustained action, is as easily administered as insulin with a minimum of discomfort, whether injected intramuscularly or subcutaneously. It is economical too, far less time and money being spent to restore the patient's working ability.

HP* ACTHAR Gel
*Highly Purified (IN GELATIN)

HP* ACTHAR® Gel is The Armour Laboratories Brand of Purified Adrenocorticotropic Hormone—Corticotropin (ACTH)

The small total dose required affords economy and virtual freedom from side actions.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY - CHICAGO 11, ILLINOIS



ELECTRON PHOTOMICROGRAPH

Diplococcus pneumoniae 35,000 x

Diplococcus pneumoniae (Streptococcus pneumoniae) is a Gram-positive organism commonly involved in

lobar—and bronchopneumonia • chronic bronchitis • mastoiditis • sinusitis otitis media • and meningitis.

It is another of the more than 30 organisms susceptible to

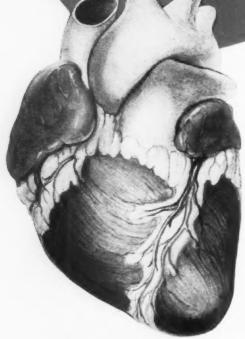
PANMYCIN

100 mg. and 250 mg. capsules

TRADEMARK, REQ. U. S. PAT. OFF.

Upjohn

THERAPY IN DEPTH



- Reduces nitroglycerin needs
- Reduces severity of attacks
- Reduces incidence of attacks
- Increases exercise tolerance
- Reduces tachycardia
- Reduces anxiety, allays apprehension
- Lowers blood pressure in hypertensives
- Does not lower blood pressure in normotensives
- Produces objective improvement demonstrable by EKG.

Descriptive brochure on request.

in angina pectoris... status anginosus

Pentoxylon—combining the tranquilizing, stress-relieving, bradycrotic effects of Rauwiloid® and the prolonged coronary vasodilating effect of pentaerythritol tetranitrate (usually abbreviated PETN)—provides a completeness of treatment heretofore unavailable to angina patients.

Therapy in depth—a wholly new principle in angina therapy—for the first time encompasses effective treatment for cause-and-effect mechanisms, which goes deeper than the superficial plane of relief afforded by simple coronary vasodilatation.

Pentoxylon is not a substitute for nitroglycerin. Continued therapy with Pentoxylon can be expected to reduce markedly or abolish nitroglycerin requirements, and greatly relieve the apprehension of the patient who lives in continuous dread of the next attack.

Each long-acting tablet of Pentoxylon contains pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid 1 mg.

Dosage: one to two tablets q.i.d., usually at mealtime and before retiring.

Available in bottles of 100 tablets.

ENTOXYLON TO

Another Riker Original

RIKER LABORATORIES, INC., LOS ANGELES 48, CALIFORNIA

MORE THAN 10 LOAVES OF BREAD

... would be required to equal the 100 mg. nicotinamide content of a single capsule of "BEMINAL" FORTE with VITAMIN C, which also supplies therapeutic amounts of other essential B factors and ascorbic acid as follows:

Thiamine mononitrate (B₁) 25.0 mg. equivalent to more than 400 eggs

Riboflavin (B₂) 12.5 mg.

equivalent to at least 8 slices of liver

Nicotinamide 100.0 mg.

equivalent to more than 10 loaves of bread

Pyridoxine HCl (B₆) 1.0 mg.

equivalent to about 14 servings of spinach

Calc. pantothenate 10.0 mg.

equivalent to almost 4 quarts of milk

Vitamin C (ascorbic acid)100.0 mg.

equivalent to more than 15 apples











"BEMINAL" FORTE with VITAMIN C



Recommended whenever high B and C levels are required and particularly pre- and postoperatively. Suggested dosage: 1 to 3 capsules daily, or more as required.

No. 817 - supplied in bottles of 100 and 1,000



ederle

ACHROMYCIN TETRACYCLINE TABLETS

A widely prescribed form of the outstanding broad-spectrum antibiotic

Sugar-coated, easy-to-swallow ACHROMYCIN Tablets are available in three potencies: 50, 100, and 250 mg.

In each of its many forms, ACHROMYCIN exhibits notable characteristics: it diffuses rapidly in body tissues and fluids; gastrointestinal irritation is rare and mild in nature.

ACHROMYCIN has proved effective against a wide variety of infections including those caused by Gram-positive and Gram-negative bacteria, rickettsia, and certain virus-like and protozoan organisms.

OTHER DOSAGE FORMS

CAPSULES: 50, 100, and 250 mg.

PEDIATRIC DROPS: (see opposite page)

ORAL SUSPENSION: (see opposite page)

SPERSOIDS* Dispersible Powder (Chocolate Flavor): 50 mg. per rounded

teaspoonful (3 Gm.), 12 and 25 dose bottles

SOLUBLE TABLETS: 50 mg.

INTRAVENOUS: vials of 100, 250, and 500 mg.

INTRAMUSCULAR: vials of 100 mg. (for dilution with 2 cc. of sterile

water or saline)

TOPICAL OINTMENT (3%): 1/2 and 1 oz. tubes

OPHTHALMIC OINTMENT (1%): 1/8 oz. tubes

EAR SOLUTION (0.5%): 10 cc. dropper bottles

TAR SULUTION

AGIRO ON GIA

ACHROMYG

ORAL SUSPENSION and PEDIATRIC DROPS



popular cherry flavor

ACHROMYCIN is available in two cherryflavored dosage forms that are highly acceptable to patients—particularly children.

The Pediatric Drops are packaged with an easy-to-read graduated dropper. The Oral Suspension, supplied as dry crystals in a 1 oz. bottle. Both Oral Suspension and Pediatric Drops, when reconstituted by the pharmacist or nurse, retain potency for two weeks at room temperature.

ACHROMYCIN, an outstanding broadspectrum antibiotic, is relatively free from untoward side reactions and provides rapid diffusion in body tissues and fluids.

ORAL SUSPENSION (Cherry Flavor): 250 mg. per teaspoonful (5 cc.), 1 oz. bottles

PEDIATRIC DROPS (Cherry Flavor): 100 mg. per cc. (approx. 5 mg. per drop), 10 cc. bottles

DIVISION LEDERLE LABORATORIES AMERICAN CHANAMINI PEARL RIVER, N.Y.

An important agent in internal medicine

THE RIKER BRAND OF RESERPINE

 In the majority of hypertensives, Serpiloid lowers tension, tranquilizes, relieves associated symptoms

and apprehension

(nonsoporific sedation)

- In the normotensive, it does not lower blood pressure significantly
- No contraindications
- For long-term use, virtually free from side actions
- Simple dosage . . . One tablet (0.25 mg.) t.i.d. Clinical samples on request.



STATEMENT OF OWNERSHIP

STATEMENT OF THE OWNERSHIP, MANAGE-MENT, AND CIRCULATION REQUIRED BY THE ACT OF CONGRESS OF AUGUST 24, 1912, AS AMENDED BY THE ACTS OF MARCH 3, 1933, AND JULY 2, 1946 (Title 39, United States Code, Section 233)

Of The American Journal of Medicine, published monthly at New York, N. Y., for Oct. 1, 1954.

- 1. The names and addresses of the publisher, editor, managing editor, and business managers are: Publisher, The American Journal of Medicine, Inc., 49 W. 45th Street, New York 36, N. Y.; Editor, Alexander B. Gutman, M.D., Mount Sinai Hospital, 100th Street & Fifth Ave., New York 29, N. Y.; Managing editor, Florence A. Wey, 49 West 45th Street, New York 36, N. Y.; Business manager, Pliny A. Porter, 49 West 45th Street, New York 36, N. Y.
- 2. The owner is: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual member, must be given.) The American Journal of Medicine, Inc., 49 West 45th Street, New York 36, N. Y.; M. T. Wisotzkey, President and Sole Owner, 49 West 45th Street, New York 36, N. Y.
- 3. The known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities are: (If there are none, so state.) None.
- 4. Paragraphs 2 and 3 include, in cases where the stockholder or security holder appears upon the books of the company as trustee or in any other fiduciary relation, the name of the person or corporation for whom such trustee is acting; also the statements in the two paragraphs show the affiant's full knowledge and belief as to the circumstances and conditions under which stockholders and security holders who do not appear upon the books of the company as trustees, hold stock and securities in a capacity other than that of a bona fide owner.
- 5. The average number of copies of each issue of this publication sold or distributed, through the mails or otherwise, to paid subscribers during the 12 months preceding the date shown above was:

(This information is required from daily, weekly, semiweekly, and triweekly newspapers only.)

M. T. WISOTZKEY, President

Sworn to and subscribed before me this 26th day of August, 1954.

ROSE V. CELENTANO **Notary Public**

[SEAL]

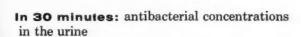
(My commission expires March 30, 1956.)

use FURADANTIN first...



TRACT INFECTIONS

for rapid clearing
of the
urine



In 24 hours: the urine is frequently clear

In 3 to 5 days: complete clearing of pus cells from the urine

In 7 days: sterilization of the urine in the majority of cases

With Furadantin there is no proctitis, pruritus ani, or crystalluria.

Average adult dosage: Four 100 mg. tablets daily, taken with meals and with food or milk before retiring.

50 and 100 mg. tablets.

Oral Suspension, 5 mg. per cc.

EATON LABORATORIES NORWICH, NEW YORK



THE NITROFURAN

A UNIQUE CLASS OF ANTIMICHOBIAL

FURADANTIN[®]
brand of nitrofurantoin, Eaton

Because it is widely known
throughout the world
and has demonstrated its
effectiveness in rapidly
controlling the great majority
of common infections,
this broad-spectrum
antibiotic is prescribed
with certainty by
physicians the world over.

terra cognita Terra

Supplied in the many convenient forms required in the practice of modern medicine: Capsules, Tablets (sugar coated), Pediatric Drops, Oral Suspension, Intravenous, Intramuscular, Ophthalmic (for solution), Ophthalmic Ointment, Ointment (topical), Vaginal Tablets, Troches, Otic, Nasal, Aerosol, Soluble Tablets and Topical Powder.

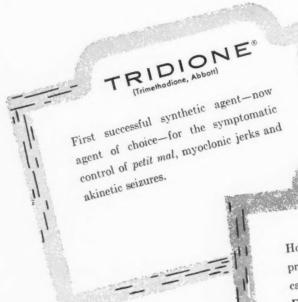


Mycin

rapid absorption
wide distribution
prompt response
excellent toleration



PFIZER LABORATORIES, Brooklyn 6, N.Y DIVISION. CHAS. PFIZER & CO., INC



Have YOU used these modern

Anticonvulsants?

If you have, you know that each-used wisely, carefully-adds inestimably to the scope and progress of treatment of various epileptic disorders. If these drugs are not yet familiar to you, we ask that you remember them. Each has signalled a dramatic advance in the field of antiepileptic medicine . . . each has specific uses, advantages. With them, you will be better able to fit your treatment to the seizure . . . individualize your anticonvulsant therapy. Write today for literature on any or all of these important anticonvulsants. Abbott Laboratories,

North Chicago, Illinois. Abbott

Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the petit mal triad.

GEMONIL®

A new drug of low toxicity for grand mal, petit mal, myoclonic and mixed seizures. Effective in conditions symptomatic of organic brain damage.

PHENURONE

A potent anticonvulsant for psychomotor epilepsy, grand mal, petit mal and mixed seizures. Often successful where all other forms of therapy have failed.



PROTAMIDE for NEURITIS

...types resistant to other therapy—where nerve root inflammation is not caused by mechanical pressure

in 80.7% of patients... 52.9% in 5 days1

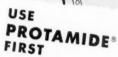


PROTAMIDE® for HERPES ZOSTER

... even cases unresponsive to a wide variety of other medications²

GOOD TO EXCELLENT RESULTS

in 82.7% of patients in two studies... 70.4% with 5 injections or less^{2,3}



...as early as possible in the course of the illness

in Neuritis - COMPLETE RECOV-

ERY IN 100% of patients when Protamide therapy was started not later than the fourth day of illness...80.3% recovering after five days of therapy.1

in Herpes Zoster - GOOD TO EXCELLENT RESULTS IN 93.3%

of patients (80% with 5 injections or less) when Protamide therapy was started during



PROTAMIDE° IS SAFE

with "no untoward reactions or evidence of toxicity"2

PROTAMIDE is a sterile colloidal solution of processed and denatured proteolytic enzyme obtained from the glandular layer of fresh hog stomach. It is supplied in boxes of ten 1.3 cc. ampuls, and the usual dosage is 1 ampul daily by intramuscular injection. Available through your regular source of supply.



MEFRENCES!

1. Smith, R. T.: New York
Med. 8:16, 1952. 2. Combes,
F. C. & Canizares, O.: New
York St. J. Med. 52:706, 1952.

3. Marsh, W. C.: U.S. Armed
Forces M. J. 1:1045, 1950.





maalox

for gastric hyperacidity in peptic ulcer

Suspension MAALOX—Rorer provides the hydroxides of Magnesium and Aluminum in colloidal form . . . pleasantly flavored and highly acceptable, even with prolonged use.

Relief of pain and epigastric distress is prompt and long-lasting.

Freedom from constipation and side effects common to other antacids is noteworthy.

supplied:

in 355 cc. (12 fluidounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension.)

Samples will be sent promptly upon request.



WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square, Philadelphia 6, Penna.
ESTABLISHED IN 1910

These are the gantrisin advantages —

Gantrisin 'Roche' is a single, soluble,
wide-spectrum sulfonamide -- especially
soluble at the pH of the kidneys. That's
why it is so well tolerated...does not
cause renal blocking...does not require
alkalies. Produces high plasma as well
as high urine levels. Over 250 references
to Gantrisin®in recent literature.

-and these are the reasons for Gantricillin

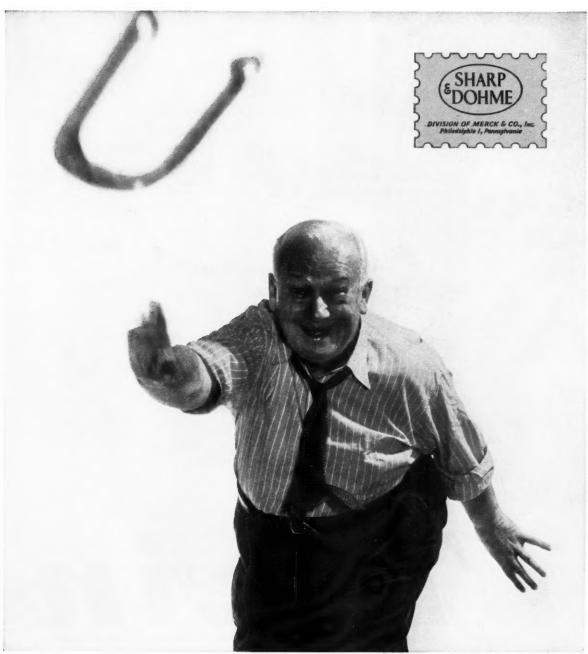
It provides Gantrisin PLUS penicillin...

for well-tolerated, wide-spectrum antibacterial therapy...in tablets of two

strengths -- Gantricillin 300 for severe

cases; Gantricillin (100) for mild cases -
and in an easy-to-take suspension for

children -- Gantricillin (acetyl)-200 'Roche.'



PHOTOGRAPH BY CHARLES KERLEE

Gives "remarkable increase in strength, vigor"1...

REDISOL

CRYSTALLINE VITAMIN B12

In "pernicious anemia or tropical sprue in relapse," not even blood transfusions give the "remarkable increase in strength, vigor and appetite," induced by vitamin B_{12} .

REDISOL—vitamin B₁₂—has hemopoeitic activity of liver²; improves neurologic symptoms; no

evidence of toxicity.² Valuable in trigeminal neuralgia to relieve pain.

Quick Information: Tablets, 25 and 50 mcg.; Injectable, 30, 100 and 1000 mcg. per cc.; Elixir, 5 mcg. per 5 cc.

References: 1. J.A.M.A. 153:185, 1953: 2. N.N.R. 1953, p. 486.



Description of tetrahydrozoline hydrochloride

nasal patency in minutes for hours

in minutes new standard

Pfizer LABORATORIES



odorless and tasteless



neither stings nor burns



almost immediate relief



does not induce rhinorrhea



action lasts longer



free from side effects



chemically new

TYZINE is a chemically unique and clinically unsurpassed nasal decongestant with proven patient-acceptance.

With TYZINE, reduction of swollen nasal mucosa is rapid, and therapeutic benefits are prolonged. Taken at bedtime, TYZINE affords relief throughout the night. And TYZINE does not produce rebound congestion or other undesirable side effects — in short—

a new standard for nasal decongestion.

Supplied: Tyzine is available in aqueous solution of 0.1% in 1-oz. bottles.

for nasal decongestion

Division, Chas. Pfizer & Co., Inc., Brooklyn 6, New York

Rauwolfia serpentina

Preparations

IN HYPERTENSION

MILD

Rautensin

SEVERE

Rauwera

Tystoserpine

RAUTENSIN In Mild and Moderate Hypertension

Each tablet contains 2 mg. of the alseroxylon fraction of Rauwolfia serpentina. The ideal Rauwolfia preparation for starting therapy in every patient.

Dose: Two tablets (4 mg.) once daily.

RAUVERA In Severe or Fixed Hypertension

Provides per tablet 1 mg. of Rautensin and 3 mg. of mixed Veratrum alkaloids (alkavervir). The safest of the more potent hypotensive combinations.

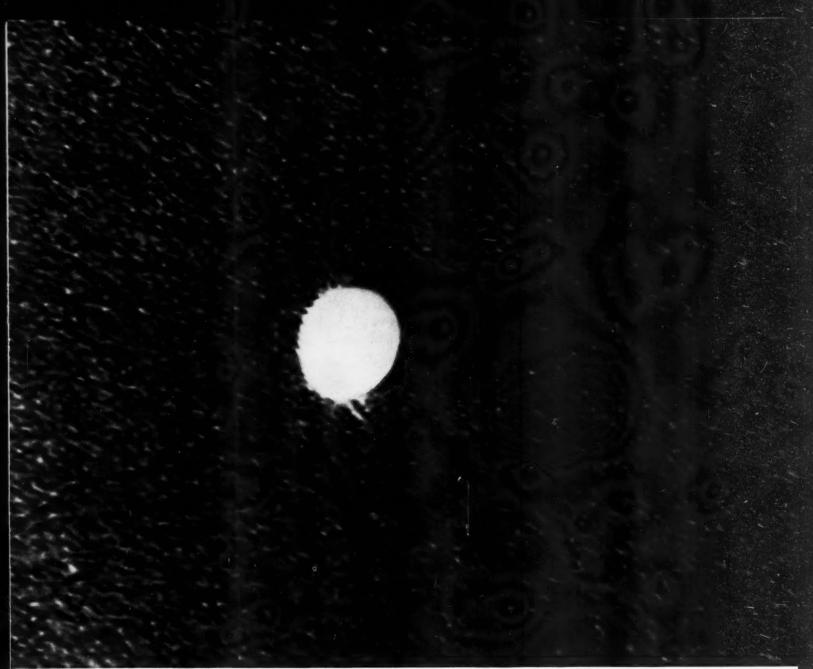
Dose: One tablet, q.i.d., p.c. and at bedtime, at no less than four-hour intervals.

CRYSTOSERPINE For Tranquilizing Sedation Without Somnolence

Each tablet contains 0.25 mg. of crystalline reserpine. Especially valuable when emotional agitation and anxiety must be controlled. Produces sedation without somnolence.

Dose: One to four tablets daily, depending on degree of sedation required.

SMITH-DORSEY . Lincoln, Nebraska A Division of THE WANDER COMPANY



ELECTRON PHOTOMICROGRAPH

Staphylococcus aureus 35,000 x

Staphylococcus aureus (Micrococcus pyogenes var. aureus) is a Gram-positive organism commonly involved in a great variety of pathologic conditions, including pyoderma • abscesses • empyema • otitis • sinusitis • septicemia bronchopneumonia • bronchiectasis • tracheobronchitis • and food poisoning

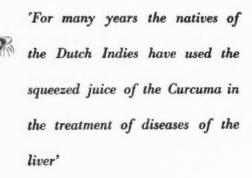
It is another of the more than 30 organisms susceptible to

PANMYCIN

100 mg. and 250 mg. capsules

#TRADEMARK, REG. U.S. PAT. OFF.

Upjohn



allogen

Gallogen (gal-o-jen) is the Massengill name for the synthesized active principle of the ancient drug Curcuma. The isolation and synthesis of the active principle permits the administration of a pure, standardized form of the drug. Gallogen is a true choleretic, not a bile salt.

Gallogen acts directly on the hepatic cells. It stimulates the flow of bile which is whole in volume and composition. The choleresis is in proportion to the functional capacity of the liver and is prompt and lasting.

Gallogen is indicated whenever it is desirable to increase the flow of bile, encourage activity of the gallbladder and promote normal function of the biliary system.

send for professional literature and sample

Supply: in bottles of 100 and 1000 tablets containing 75 mg. of the diethanolamine salt of the mono-d-camphoric acid ester of p-tolylmethyl carbinol.

CLINICAL REPORT ON ANSOLYSEN . . . NEW ANTIHYPERTENSIVE AGENT

ANSOLYSEN—pentolinium tartrate—is a potent ganglionic blocking agent which presents the advantage of comparative freedom from by-effects. This effective hypotensive agent is recommended for use in patients with moderate to severe hypertension.

Comparing the effects of hexamethonium and ANSOLYSEN in 27 patients with severe "fixed" hypertension, Freis and coworkers¹ observed:

ANSOLYSEN was approximately five times more potent than hexamethonium

ANSOLYSEN produced less tolerance

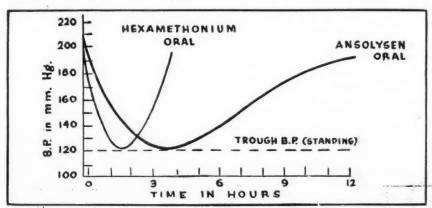
ANSOLYSEN's hypotensive effect was 40% longer

ANSOLYSEN's hypotensive effect was more predictable

ANSOLYSEN caused less pronounced by-effects

ANSOLYSEN caused less constipation

ANSOLYSEN lowered the blood pressure significantly, with little or no risk of producing collapse reactions or paralytic ileus



Changes in blood pressure noted by Smirky after therapeutic oral doses of hexamethonium and ANSOLYSEN.

Supplied: Scored tablets--40 and 100 mg., bottles of 100 $\,$

Injection-10 mg. per cc., vials of 10 cc.

1. Freis, E. D., and others: Circulation 9:540 (April) 1954

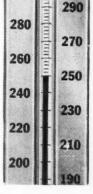
2. Smirk, F.H.: New Zealand M.J. 52:1 (Oct.) 1953

ANSOLYSEN'

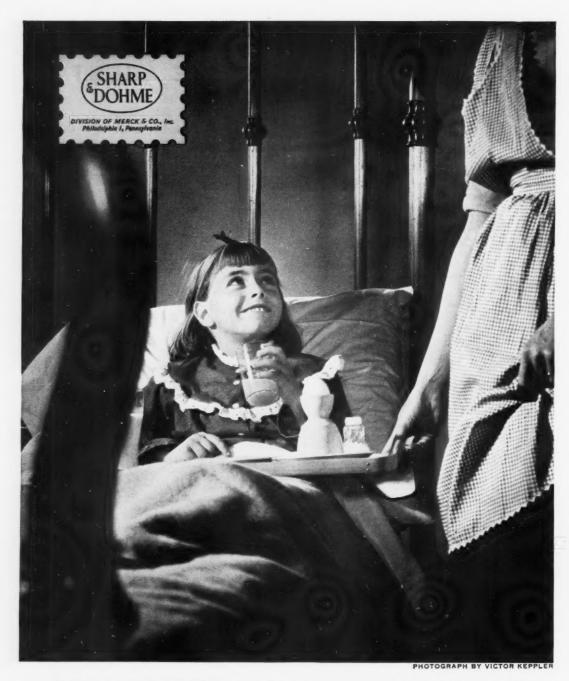


PENTOLINIUM TARTRATE

*Trademark



300



"Now I can swallow easily—my throat's much better"

TRACINETS

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

Your patients will like TRACINETS because they really soothe irritated throats—taste good, besides.

Two topical antibiotics combined, bacitracin and tyrothricin, give your patients double antibacterial action, while benzocaine provides a soothing, anesthetic effect. In severe throat infections, TRACINETS conveniently supplement systemic therapy.

Quick Information: Each troche contains 50 units of bacitracin, 1 mg. of tyrothricin, 5 mg. of benzocaine. In vials of 12.

Add(Q) (1) Inde

The Amour Department Agent Appear Laborated

Remarks Welliams A. C. (1967)
Control of the Control of Control of

The Bream of the Market Barrier Barrie

Rollmann-Lauren, krif (*) Geografischer (*) (*) Lauren Giffe (*)

The B. R. Me Co.
Chamon, Inc.
Parke, Lavis
Chamon Division of Co.

A. H. Robins Co. Lice.

J. B. Robins of Market Mark

O. D. Starte & Co.
Sharp J. Dohne, Division of Merce & Co., 44
Sherp J. L. Martine

A R. Squibb to Seas Div 1 and Malviera Goden of Cornel C. Vindian Co.

Water Laboratorestand
Water Laboratorestand
Warner-Chileses thanks: send. Can.
White Section 100.